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ORIGINAL ARTICLES

EFFECT OF GLUCOCORTICOID HORMONES ON EXPERIMENTALLY INDUCED ALLERGIC REACTIONS ON HUMAN SKIN

A Histologic and Histochemical Study

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EXPERIMENTALLY produced skin allergic reactions on human beings have a histologic basis similar to those seen in experimental animals.[1-6] Moreover, the macro- and microscopic similarity to the wheals obtained with the intradermic injection of histamine is also well known.[7-11]

The inhibitory action of ACTH and corticoids in different allergic conditions have been proved,[12, 13] but this is not so in regards to experimentally produced skin allergic reactions[14] or wheals caused by histamine.[15] To substantiate the apparent absence of hormonal effects in these latter conditions, it was considered that a careful study of the tissues at the microscopic level was necessary. For this reason we have carried out a histologic and histochemical study of the wheals produced by histamine and specific allergens before and after the administration of glucocorticoid hormones, either by mouth or by local treatment of the skin.

MATERIAL AND METHODS

Fifty allergic patients, divided into two different groups, were studied. Their only ostensible clinical manifestations were either seasonal rhinitis or asthma that had been proved to be of pollenic etiology. Only those showing constant and easily reproducible wheals were included in the group under study.

The first group was composed of 21 patients who were treated with prednisolone by mouth. Of these, 9 were males and 12 females, and their

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ages ranged between 27 and 52 years; the majority were from 32 to 44 years of age. They were given prednisolone for a period from 1 to 30 days (1 day —2 cases; 2 days—2 cases; 10 days—4 cases; 20 days—4 cases; 30 days—9 cases). Half of the patients in each period received a daily minimum dose of 10 mg. and the other half a maximum daily dose of 30 mg.

The second group, including 29 patients, was treated with topical application of ointments on a given area three times daily. Ten were males and 19 females whose ages ranged from 25 to 51 years, the majority were between 28 and 40 years of age. They were treated in the following way: (a) 10 patients with 0.5 per cent chloral hydrate of diethylaminoacetate of hydrocortisone from 1 to 3 weeks (first week—3 cases; second week—4 cases; third week—3 cases); (b) 11 patients with 1 per cent hydrocortisone acetate from 2 weeks to 9 months (2 weeks—1 case; 1 month—1 case; 2 months—1 case; 3 months—4 cases; 5 months—2 cases; 9 months—2 cases); (c) 8 patients with 1 per cent prednisolone from 2 to 6 months (2 months—1 case; 3 months—2 cases; 4 months—3 cases; 6 months—2 cases).

In both groups, before and after treatment, three separate intradermic wheals were made in the form of an arrow in each patient in the middle of the anteroexternal region of the thigh, about 6 to 8 cm. apart. Each wheal was provoked by using 0.10 c.c. of saline solution as a control in the first, 0.10 c.c. of histamine in the second, and 0.10 c.c. of a pollen solution in the third. The amount of histamine applied varied between 1 and 20 gammas, according to the reactivity of each patient. Pollen from maple and plane trees, gramineous and Compositae was used in quantities, varying from 2 to 200 Noon units, according to the patient's sensitivity. In patients treated with corticoid ointments the wheals were made in a restricted marked area, which had been previously topically treated.

Thirty minutes after the intradermic injection, the wheals were measured and, under ethylchloride local anesthesia, a biopsy of each one was made. The skin thus obtained was cut into two parts, one being placed in Bouin's solution and the other in 10 per cent buffered formol for 24 hours. Serial sections were obtained from each biopsy and the following histochemical and histologic techniques were applied: (1) for general morphology—hematoxylin-eosin and Heidenhain-azan; (2) Weigert's method for elastic fibers; (3) Hortega's silver impregnation method for collagenous and reticular fibers; (4) Hortega's panoptic silver technique for cellular morphology; (5) mucopolysaccharides were stained with 0.055 per cent toluidine blue at pH 3.5 and Alcian blue, controlled by incubation in hyaluronidase (30 TRU per c.c.) at 37° C. for 3 and 24 hours; (6) nucleoproteins with 0.055 per cent toluidine blue at pH 4.7 controlled by incubation in 0.1 per cent ribonuclease (Nutritional Biochemical) at 37° C. for 30 and 60 minutes; also, with the use of this technique, metachromatically stained mast cells were demonstrated; (7) PAS technique controlled with ptyaline and methanol-chloroform for polysaccharides, basement membranes, and reticular fibers.

RESULTS

Tolerance to the treatment was very good, there being no noticeable side effects; only moderate signs of artificial hypercorticalism developed in patients given the hormones by mouth.

No changes were observed in any case in the wheals induced before treatment when compared with the macroscopic aspect and measurement of those obtained in the same patient after treatment with prednisolone by mouth, whatever the period of administration or the dosage of corticoid used. In the second group, those treated with corticoid ointments in which chloral hydrate of diethylaminoacetate of hydrocortisone was used, the histamine and pollen wheals showed a less prominent and less congestive papule. Conversely, no appreciable changes were found in patients topically treated with hydrocortisone and prednisolone.

In spite of the absence of macroscopic changes, the major part of the biopsies showed variable degrees of histologic and histochemical modifications after the hormonal treatment. In the first group of cases, this was in direct relation to the different doses used and the length of time administered. Doses of 10 mg. daily for 10 to 20 days produced no changes, but these were noticeable at 30 days. Doses of 30 mg. during 1, 2, and 10 days produced no changes at all but at 20 and 30 days these were evident. In total, 8 patients showed no histologic changes, 8 showed moderate changes, and in 5 slight changes were present.

In the second group of patients, the histologic and histochemical changes were directly related to the type of corticoid used and the time during which it was administrated. With chloral hydrate of diethylaminoacetate of hydrocortisone ointment, no changes appeared when it was used for 1 or 2 weeks, but moderate changes were detected after 3 weeks. No changes whatsoever were noticed in those patients who had used hydrocortisone for 2 to 4 weeks, but some changes took place after 2 months, and this became quite evident after 5 months of treatment. The prednisolone ointment caused no changes during the first 2 or 3 months; however, some changes could be seen at 4 months and become noticeable after 6 months of treatment. In total, there were 7 cases with no modifications at all and 3 with moderate changes with the use of chloral hydrate of diethylaminoacetate of hydrocortisone. Where hydrocortisone was used, 4 patients showed no changes at all, 5 showed moderate changes, and evident changes could be seen in 2. With prednisolone, 4 patients remained the same, 2 showed moderate changes, and 2 intense changes.

To evaluate the already mentioned microscopic modification observed in the wheals after treatment, two main structural components of the allergic inflammation were taken into account: (1) the *vascular reaction* which includes congestion, hypertrophy of the endothelium, leukocytic (mainly eosinophils) and serous exudation; (2) the *changes in the neighboring connective tissue* which comprised intercellular edema, alterations of fibroblasts,

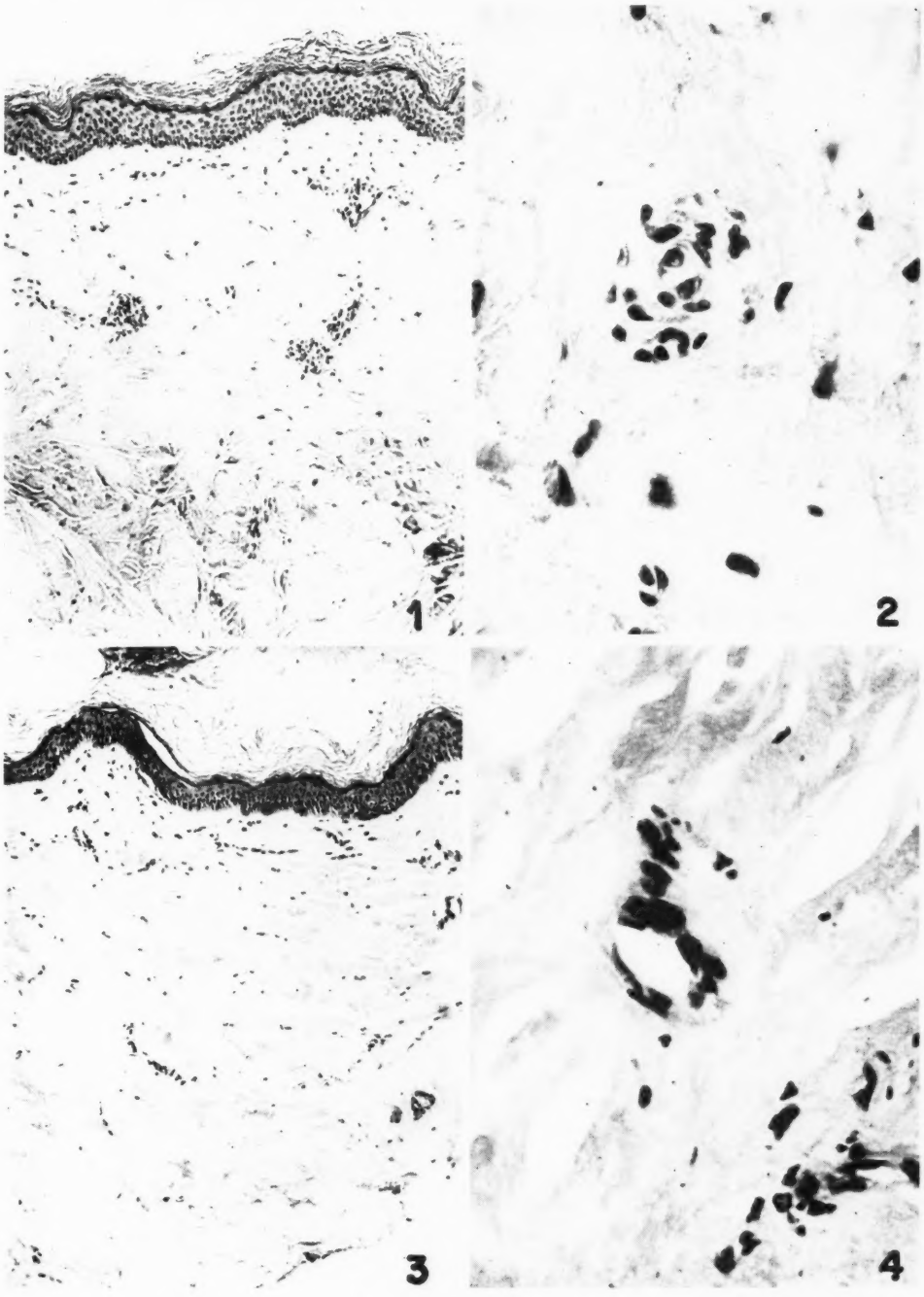
mast cells, collagenous and elastic fibers, mucopolysaccharides of the amorphous substance, and basement membrane of the adjacent epithelium. As there were no remarkable differences in the results obtained either in the histamine or pollen wheals, Table I shows detailed results in both types before and after treatment.

TABLE I. ACTION OF GLUCOCORTICOID HORMONES ON POLLEN AND HISTAMINE WHEALS

STRUCTURAL COMPONENTS OF WHEALS	BEFORE HORMONAL TREATMENT	AFTER HORMONAL TREATMENT
Vascular Reaction		
Congestion	Intense	Diminished
Hypertrophy of endothelium and edema of the wall	Intense	Diminished; dissociation of reticular fibers
Serous exudate	Intense	Diminished
Cellular exudate	Abundant neutrophils and eosinophils	Few cells found
Alterations of the Dermal Connective Tissue		
Edema	Intense and interfibrillar	Diminished
Fibroblasts	Normal appearance; in part hypertrophic	Smaller number; in part atrophied
Mast cells	Normal appearance; some are degranulated	Degranulation and vacuolization in most of them
Collagen fibers	Edematous due to serous imbibition	Less edematous; partial dissociation
Elastic fibers	Normal appearance, slightly separated	Thicker and fragmented
Mucopolysaccharides	Normal amount and distribution	Diminished
Basement membrane	Nitid and continuous	Attenuated and sometimes discontinuous

TABLE II. ACTION OF GLUCOCORTICOID HORMONES ON CONNECTIVE TISSUE OF SALINE-INDUCED WHEAL

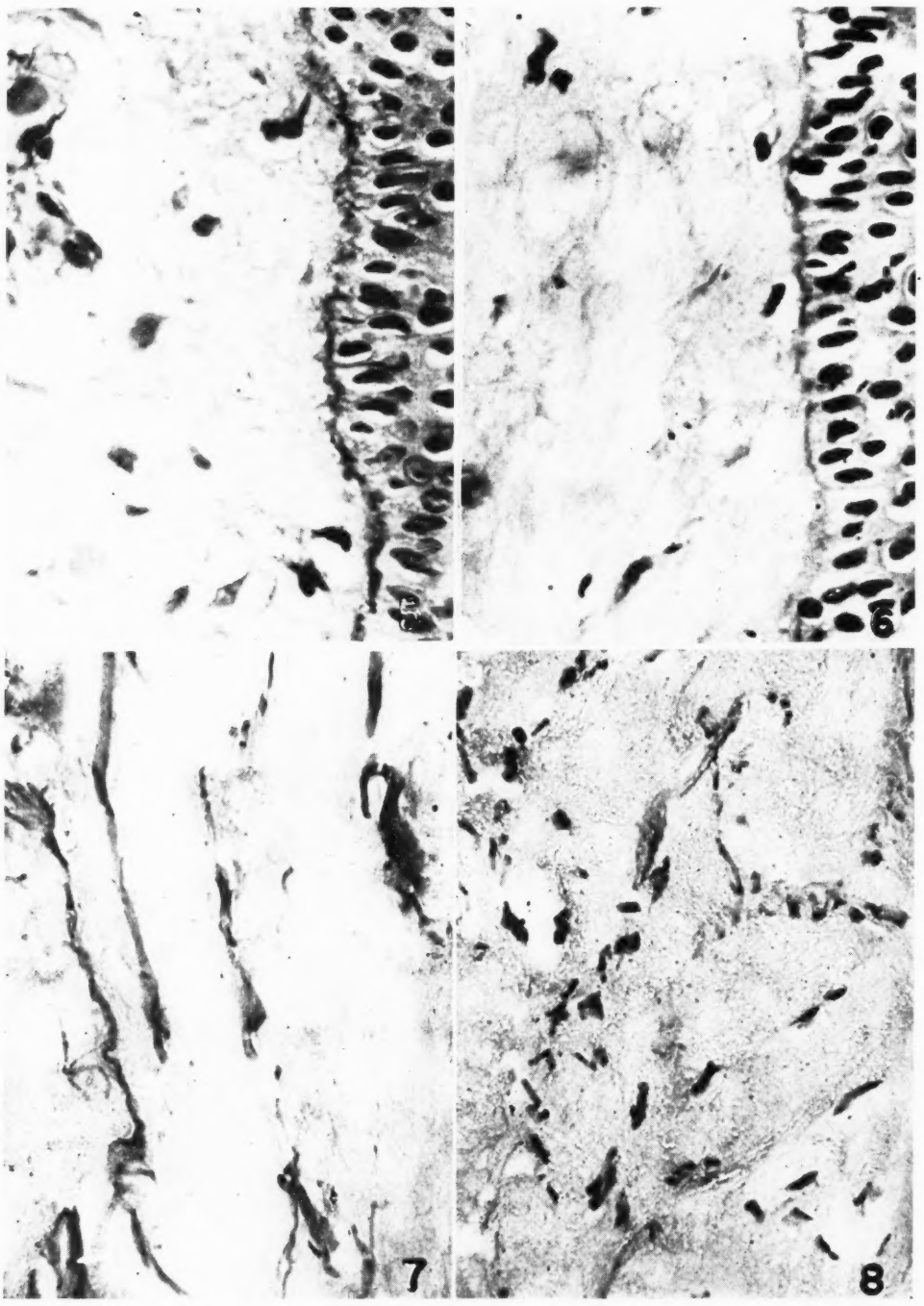
STRUCTURAL COMPONENTS OF CONNECTIVE TISSUE	BEFORE HORMONAL TREATMENT	AFTER HORMONAL TREATMENT
Fibroblasts	Normal appearance	In part atrophied and pyknotic
Mast cells	Normal appearance	Degranulation and vacuolization in some
Collagen fibers	Normal appearance	Partial dissociation
Elastic fibers	Normal appearance	Thicker and fragmented
Mucopolysaccharides	Normal amount and distribution	Diminished
Basement membrane	Nitid and continuous	Attenuated and sometimes discontinued
Blood vessels (capillaries and arterioles)	Normal appearance	Loosening of network of reticular fibers



Figs. 1-4.—Biopsies of saline-induced wheals before and after treatment with prednisolone for 4 weeks.

Figs. 1 and 2.—Before treatment. Note the normal aspect of dermal connective tissue and of an arteriole. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced 1/5.)

Figs. 3 and 4.—After treatment. Dissociation of collagen fibers and bundles and partial atrophy of fibroblasts. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced 1/5.)



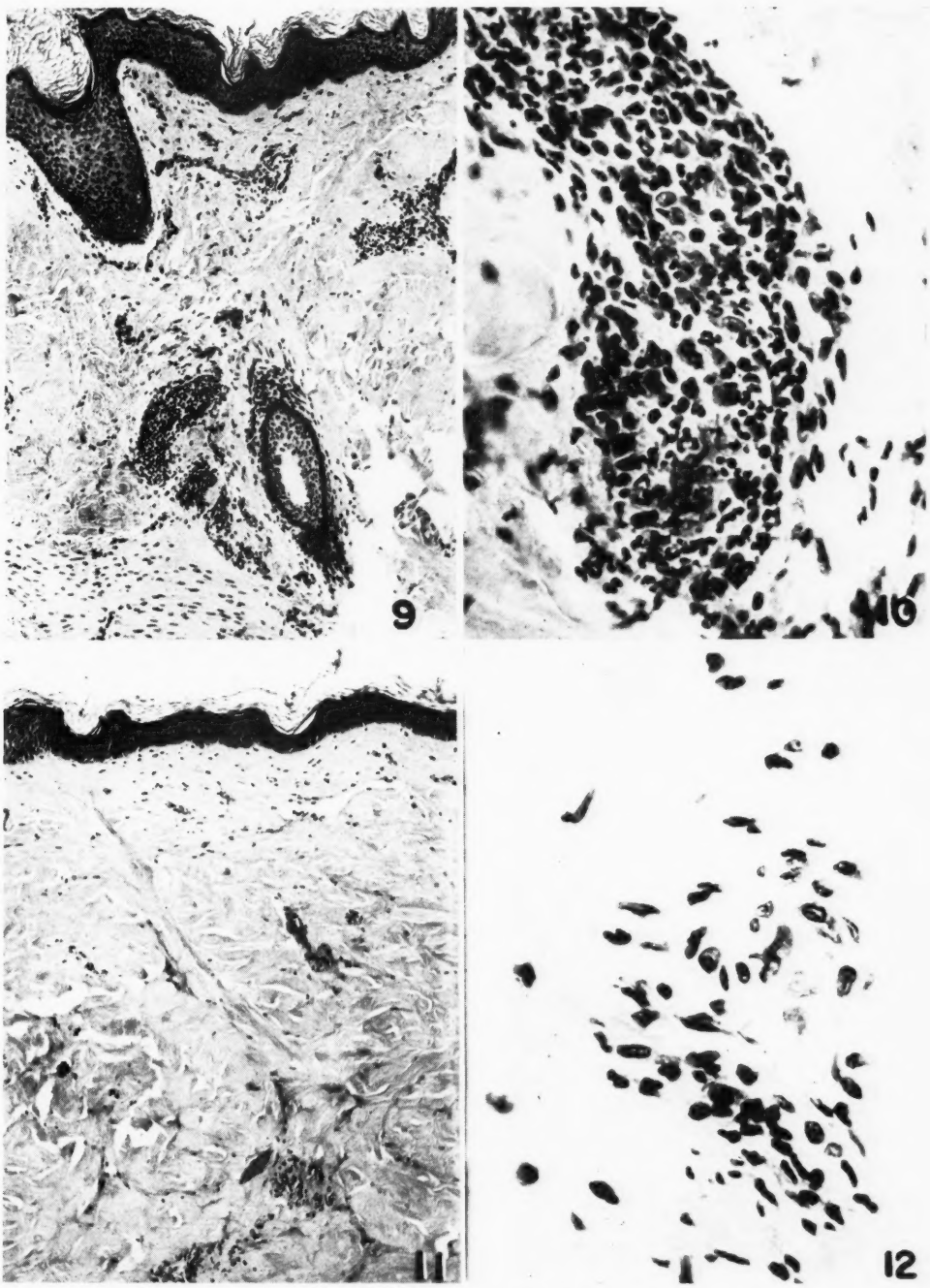
Figs. 5-8.—Biopsies of saline-induced wheals before and after treatment with prednisolone for 4 weeks.

Fig. 5.—Before treatment. Normal basement membrane and collagen fibers of papillary layer demonstrated with PAS technique; counterstaining with hematoxylin and eosin; ×700, reduced 1/5.

Fig. 6.—After treatment. Thinner basement membrane and loose connective tissue fibers of dermis. PAS technique, counterstaining with hematoxylin and eosin; ×700, reduced 1/5.

Fig. 7.—Before treatment. Normal elastic fibers of reticular layer of dermis. (Orcein; ×700, reduced 1/5.)

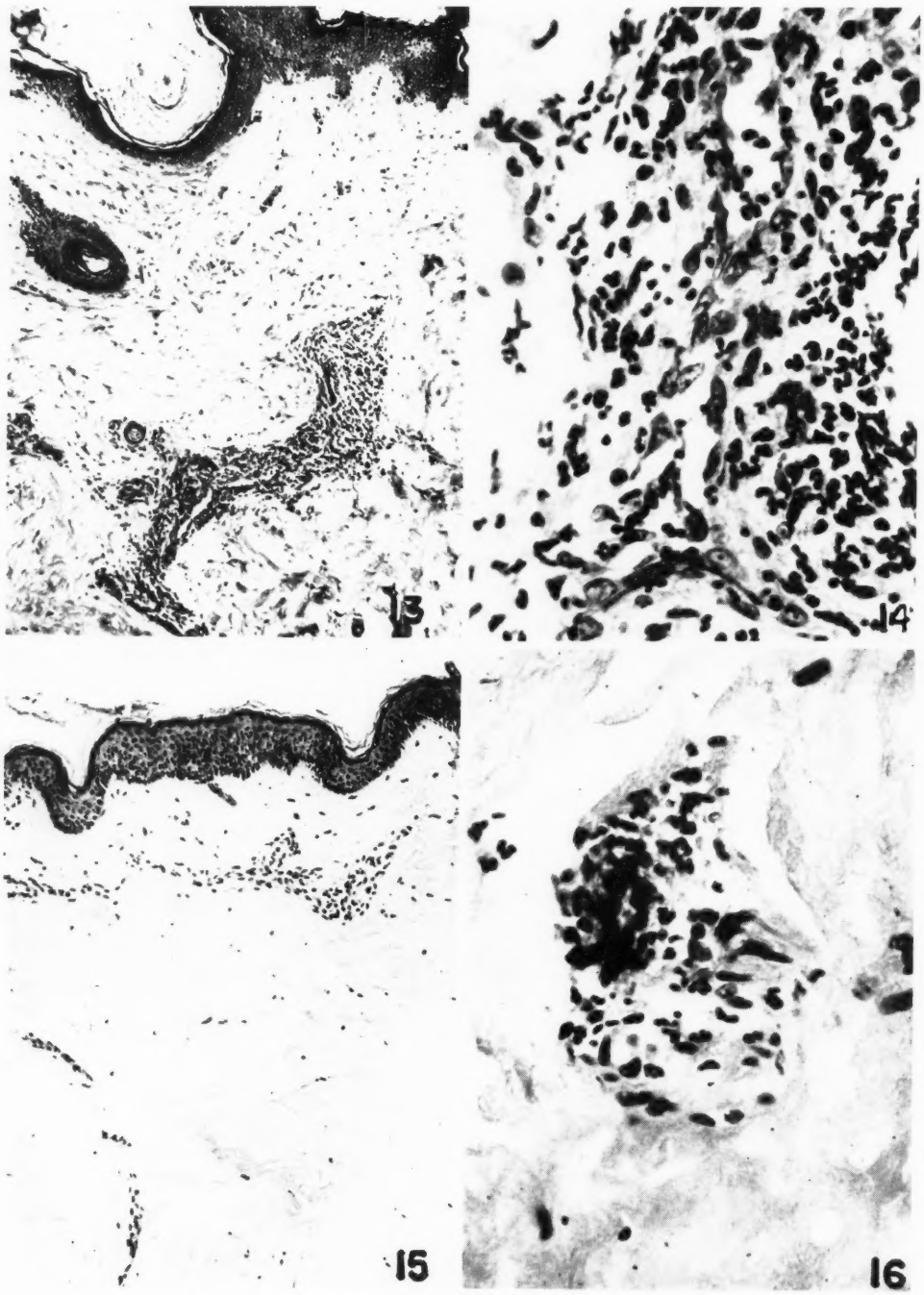
Fig. 8.—After treatment. Fragment elastic fibers of the dermis (Orcein; ×700; reduced 1/5.)



Figs. 9-12.—Biopsies of pollen-induced wheals before and after treatment.

Figs. 9 and 10.—Pollen-induced wheal before treatment. Congestion, exudation, and edema of the dermis. Cellular exudate around vessels. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced 1/5.)

Figs. 11 and 12.—After treatment. Less congestion, exudation, and edema of connective tissue. Reduced cellular exudate around vessels. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced 1/5.)



Figs. 13-16.—Biopsies of histamine-induced wheals before and after treatment.

Figs. 13 and 14.—Histamine-induced wheal before treatment. Congestion, exudation and intense edema of connective tissue. Tumefaction of the wall of the vessels and cellular exudate. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced $\frac{1}{5}$.)

Figs. 15 and 16.—After treatment. Reduced vascular reaction, connective tissue edema, and cellular exudate. (Hematoxylin and eosin; ×120 and ×700, respectively; reduced $\frac{1}{5}$.)

In regard to the saline-induced wheals used as controls, the microscopic changes brought about by hormones on the structures of normal connective tissue of dermis were equally dependant on the dosage and length of time of administration; they are described in Table II. It should be borne in mind that obviously these changes were also developed by the dermal tissue of neighboring skin in which histamine or pollen wheals were induced at the end of the treatment.

DISCUSSION

Our studies mostly confirm other authors' statements that provoked pollen and histamine skin reactions are not ostensibly modified macroscopically after the administration of corticoids. Nevertheless, the present investigation demonstrates, in the major number of cases, an inhibitory action on the allergic reaction at the histologic level and, also, that a partial involution of normal connective tissue was observed in the control saline wheal.

These effects of the glucocorticoid hormones depend, in general, on the dosage and length of time of administration, either by mouth or topically applied. The higher the dose and the longer the treatment, the more intense the inhibitory action. Even with the higher doses, 4 weeks of treatment by mouth or several months topically applied, are needed. The exception was in favor of the ointment containing chloral hydrate of diethylaminoacetate of hydrocortisone,[16] which proved to be more active than prednisolone and hydorcortisone acetate, even at a similar concentration. Changes in the wheals could be shown at the end of the third week. The modifications of the saline-induced wheals after both kinds of treatment were also paralleled by the amount and length of time of administration of hormones. Even in those patients where the allergic and histamine wheals were not modified, the corresponding saline-induced wheal invariably exhibited the complete picture of regressive changes. In no case could a separate effect on either of the wheals, whether allergic or caused by histamine, be observed; it was noted, when present, in both types of wheals.

In regard to the nature of the microscopic results, whether obtained by local or oral treatment, they were qualitatively similar in the three types of wheals. Therefore, the mechanism of action of the glucocorticoid hormones could be counted as direct.

The inhibitory effect, although always of a slight or moderate degree, consists essentially in a decrease in the intensity of congestion and edema of wall of minute vessels and of the serous and cellular exudate. In this respect not much difference was found between the wheals caused by the allergens and those caused by the histamine. There was also a marked attenuation of the edema in the surrounding connective tissue and a simultaneous regression of almost all its structures, such as, partial atrophy in most of the fibroblasts and mast cells, dissociation of collagen fibers, fragmentation of the elastic fibers, disappearance of the interfibrillar mucopoly-

saccharides, and loosening of the network of reticular fibers in the wall of small arterioles and in the basement membrane of the epithelium. On the other hand, the only remarkable changes noticeable in the saline-induced wheals were the purely involutive ones of the structures of the dermal connective tissue. This histologic picture, which agrees with previous findings on the effects of glucocorticoids on the skin of animals[17] and of normal subjects,[18] was present in the rest of the dermal skin. Therefore, the allergic and histamine wheals induced after treatment were developed on an abnormal anatomic substrate, which gives support to a possible explanation on the mechanism of action of glucocorticoids on the experimentally induced skin allergic reactions. As it was demonstrated, these hormones can affect the level of circulating antibodies but not that of reagins.[19, 20] Although two other ways might be involved, one could be referred to some disturbance in the production and/or liberation of histamine,[21-25] and the other one to the relative inability of the vessels and connective tissue structures to react adequately to histamine-like substances. Both hypotheses could be related to the presence of degranulated mast cells, alteration of the walls of vessels, partial atrophy of the fibroblasts, and involution of intercellular substance of dermal skin, as a consequence of treatment with glucocorticoids.

Other reports on the effect of these hormones on the biology of connective tissue may have some connection with the results of our study, such as the inhibition of the fibroplasia of dermal skin,[26] the partial regression of the lesions in scleroderma,[18, 27, 28] the increase in the capillary resistance,[29-32] the inhibition of provoked inflammation,[33, 34] and the arrest in the development of normal connective tissue.[35-38] On the basis of these facts, we may finally assume that the inhibitory effect of glucocorticoids on experimental allergic reactions could be due to a previous intense and long action of these hormones on the connective tissue, which as a consequence would modify its reactivity to the injury.

SUMMARY

Histologic and histochemical study of wheals induced by saline solution, pollen, and histamine, were made in allergic patients before and after the oral administration of prednisolone and topical application of different corticoids. Negative results were obtained with daily doses of 10 mg. of prednisolone for from 10 to 20 days, but moderate changes appeared after 30 days. They were noticeable when daily doses of 20 mg. were given for periods of 30 days and after 20 days with doses of 30 mg. Topically applied 0.5 per cent chloral hydrate of diethylaminoacetate of hydrocortisone showed microscopic modification after 3 weeks; with 1 per cent hydrocortisone ointment, these were noticed after 2 months of treatment, and only after 4 months when 1 per cent prednisolone ointment was used. As compared with the wheals induced before treatment, the changes were qualitatively similar in both histamine and pollen wheals and consist of (a) diminution of congestion and of the serous and cellular exudate, (b) dissociation of collagen fibers and

fragmentation of elastic fibers of dermal connective tissue, (c) atrophy in part of the fibroblast cells, degranulation, and partial vacuolization of the mast cells, reduction of the mucopolysaccharides, and discontinuity of the basement membrane of epidermis. In the saline-induced wheals, the only noticeable changes were those of partial regression of the cellular and extracellular constituents of dermal connective tissue.

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BLOOD EOSINOPHILIA AND TRANSITORY PULMONARY INFILTRATIONS ASSOCIATED WITH CARDIAC INVOLVEMENT

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SINCE Loeffler[10] first reported the syndrome of transient pulmonary infiltrations and blood eosinophilia in 1932, there have been numerous reports of similar cases.[3, 4, 12] Many cases reported in subsequent years fit the original description by Loeffler as to the benign course and short duration. Gradually, however, cases have been included in which the morbid changes persisted for months and years[1] and in which the course was malignant with widespread changes in other organs. Cases accompanied by most variable symptoms, such as the alveolar-capillary block syndome[6] and even cardiac involvement,[9] have been presented in the literature.

This article reports 3 cases of blood eosinophilia and transitory pulmonary infiltrations in which there was evidence of cardiac involvement. The previous literature will be reviewed in relation to similar cases, Loeffler's syndrome, and periarteritis nodosa.

CASE REPORTS

CASE 1.—A man, born in 1939, had a history of cough, expectoration, marked wheezing, and nasal discharge since 1956. There was no family history of allergic diseases. His increasing asthmatic symptoms necessitated hospital treatment for the first time in 1956. Prior to admission he had been treated at the outpatient department with mild antiasthmatic drugs. Respiratory tract infections, especially sinus infections, seemed to precipitate attacks of bronchial asthma. In 1956, chest x-ray studies and electrocardiograms were normal. X-ray examination of the sinuses disclosed pansinusitis. Physical examination of the heart failed to show any abnormality. Tests for allergy were normal. The blood count showed a normal white cell count with moderate esoinophilia (9 per cent).

In August, 1957, the patient was readmitted for bronchial asthma of increasing severity and bronchitis with purulent expectoration. Physical examination showed signs of marked asthmatic distress. The chest was barrel-shaped and hypersonorant to percussion. On auscultation, inspiration was weak, and a large number of sibilant and sonorous râles was heard throughout the chest. Blood pressure was 125/85 mm. Hg. During the first weeks in hospital there was no improvement of the patient's condition in spite of intensive treatment with antibiotics and antiasthmatic drugs. There was a marked tachycardia and moderately elevated temperature and erythrocyte sedimentation rate. The white cell count showed an increasing number of eosinophils (Fig. 1). A chest roentgenogram showed patchy opacities throughout the lower lung fields. An electrocardiogram showed widespread S-T elevations and a left intraventricular conduction defect (Fig. 2). A short trial with ACTH (20-10 units

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per day) was followed by a dramatic response, signs and symptoms of asthma disappeared; the temperature returned to normal, the heart rate declined, and the lung fields cleared. The electrocardiographic picture returned to normal. When, after some time, an attempt was made to withdraw ACTH medication, all the previous symptoms recurred after 4 days, with the onset of fulminant status asthmaticus, new areas of bilateral, patchy, parenchymal shadows on the chest roentgenogram and pathologic ECG changes. Resumption of ACTH therapy brought about the same dramatic relief. The same course of fulminant symptoms

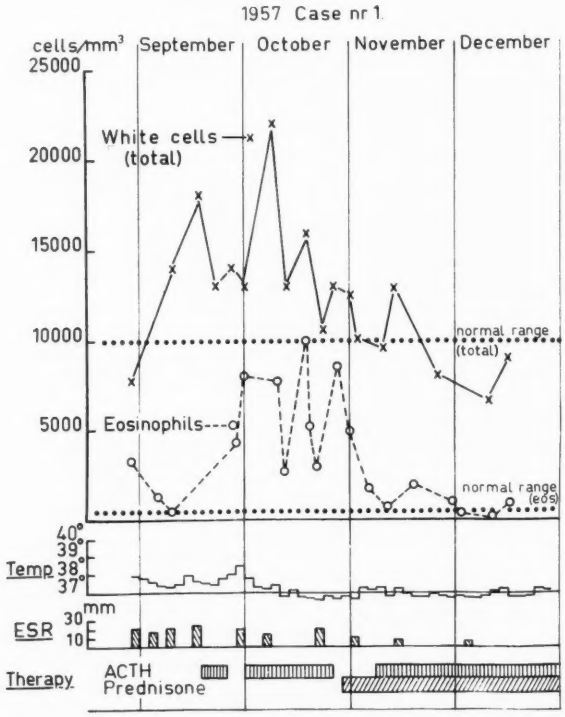

Fig. 1.—Diagram which shows white blood cell count, temperature (degrees C.), erythrocyte sedimentation rate (mm./hr.), and effect of therapy in Case 1.

recurred when the medication was again terminated. Treatment with prednisone (5-10 mg. daily) was now tried first, but without effective response. For the next 2 months the patient had to be given a combination of ACTH (10 units every other day) and prednisone. At the present time the patient is still on 10 mg. prednisone a day. This medication keeps the patient free of symptoms. He has been back at work since the spring of 1958.

In March, 1960, the patient was readmitted for observation with reference to additional treatment with steroids. Twenty-four hours after withdrawal the patient developed status asthmaticus and the eosinophil count rose from normal values to 1,450 cells per cubic millimeter. Prednisone alone brought the situation under control. Exercise tolerance test was normal. Spirometry (1961) disclosed abnormal findings consistent with marked emphysema (total lung capacity, 8,000; vital capacity, 3,700 ml.).

Laboratory Studies.—Hemoglobin was 15 to 16 Gm. per 100 ml.; repeated serum protein determinations and paper electrophoresis showed a normal pattern, without elevation of the γ-globulin fraction. Sputum culture revealed *Hemophilus influenzae* and *Staphylococcus aureus*. Several sputum specimens were negative for acid-fast bacilli and negative on inoculation into guinea pigs. Analysis of urine for sugar and protein was negative on several occasions. The total count of eosinophils was determined according to Rud.[14] The L.E. cell test was negative on several occasions. Sternal marrow biopsies showed unspecific find-

ings with a predominance of matured eosinophils. Biopsy from skin, lymph nodes, and calf muscle revealed a normal histologic picture. Serologic tests for syphilis and Salmonella infections were nonreactive. Frequent examination of stool specimens failed to show parasites or ova. Heart volume has been normal since 1956 (390 to 430 ml./M.^{2}).

CASE 2.—A woman, born in 1931, had a family history of bronchial asthma and eczema. As a child, she had frequent attacks of urticaria and allergic rhinitis. Since 1958, symptoms of bronchial asthma had occurred during the course of respiratory tract infections and with attacks of sinusitis. Hospital treatment became necessary three times during 1958 and 1959.

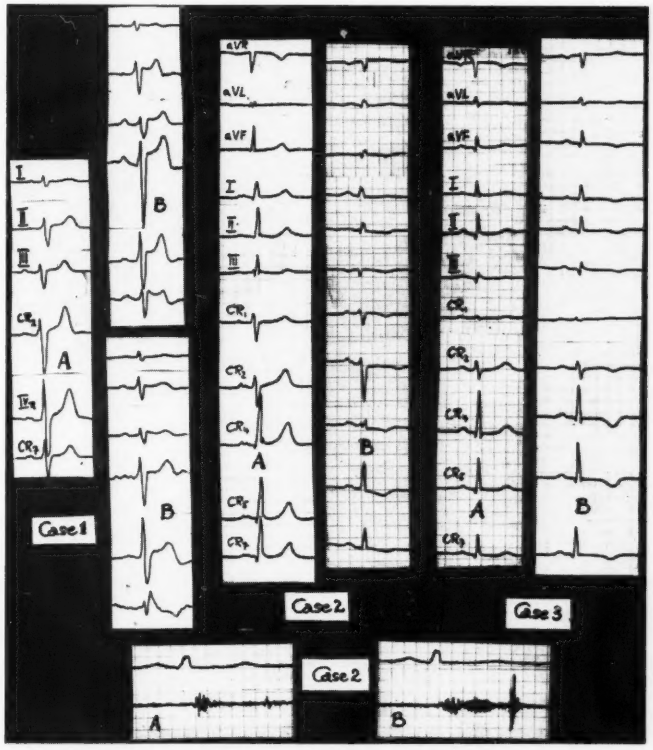

Fig. 2.—Electrocardiographic tracings prior to onset of eosinophilia *(A)* and during attack *(B)*, as well as a phonocardiogram from Case 2 (stethoscopic frequency response).

During attacks, physical signs of bronchial obstruction were found. After the first admission, long-term steroid treatment with prednisone was instituted, supported by antibiotics on appearance of infections. Allergy tests were negative. Repeated roentgenograms of the lungs and heart were all normal until 1960; several normal electrocardiograms were obtained during this period also. White cell counts revealed an eosinophilia of about 20 per cent in 1958 and 15 per cent in 1959. The patient was re-examined regularly at the out-patient department.

In May, 1960, the patient was readmitted to the hospital with numbness and increasing pains in the right leg. There were no asthma or cardiac symptoms on admission. The blood pressure was 125/70 mm. Hg. During the first weeks further impairment of sensation developed. Moreover, a marked tenderness of the feet, thighs and the right forearm occurred, together with foot and wrist drop on the right side, i.e., signs of polyneuritis. From admission to the end of May the patient complained of weakness, had a slightly elevated temperature, and a marked eosinophilia (Fig. 4). There were no abnormal physical signs from heart or lungs. Two chest roentgenograms showed normal findings. During the first days of June the temperature, white blood cells, and eosinophils reached higher values than

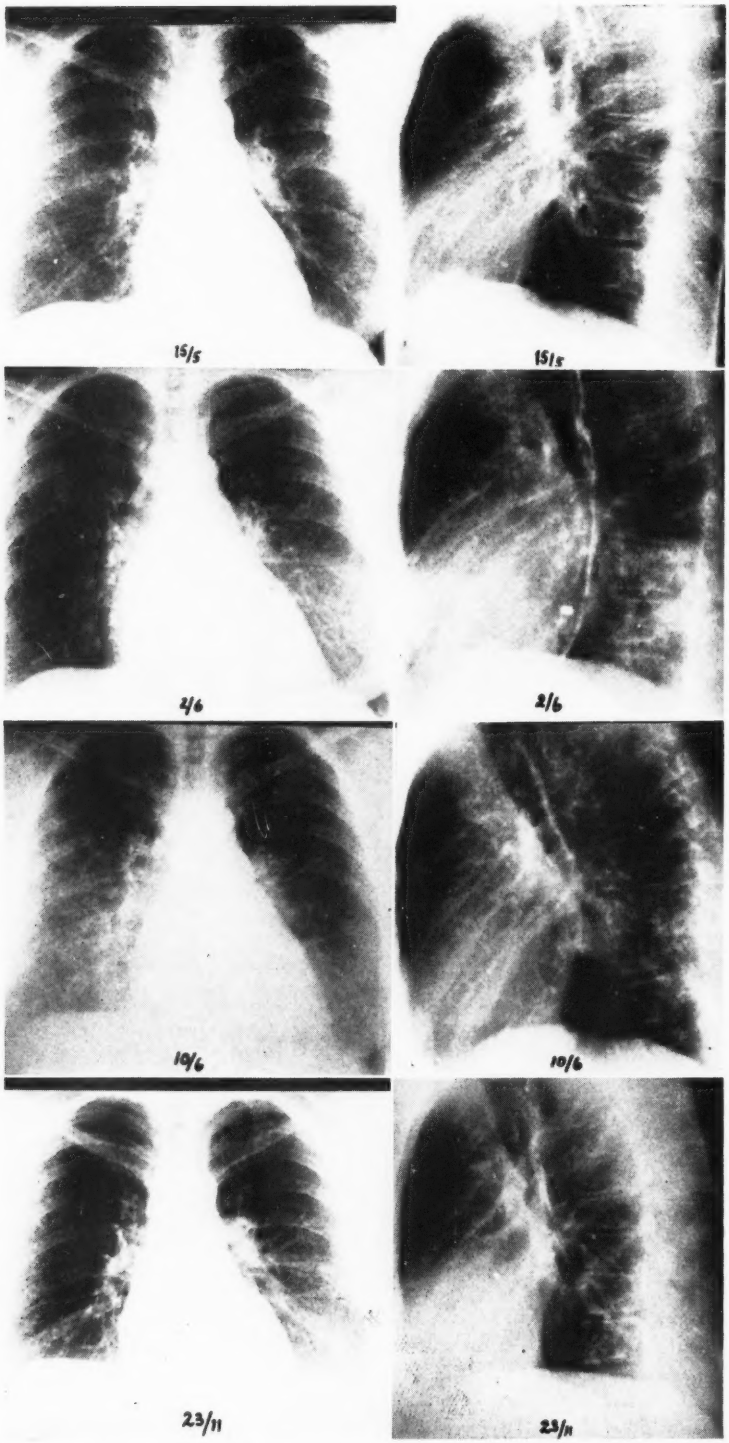

Fig. 3.—Some representative chest roentgenograms of Case 2 which illustrate the transitory infiltrations in the lung fields and the enlargement of the heart outlines and their regression. Total heart volumes: 15/5 = 700 ml., 2/6 = 850 ml., 10/6 = 960 ml., and 23/11 = 580 ml.

before. The patient's clinical condition was severely aggravated, and she complained of palpitation and precordial pain. Physical examination revealed a soft systolic murmur confirmed by phonocardiogram; the pulse rate was 120. A chest roentgenogram of the lungs showed confluent, ill-defined infiltrations, involving posterior parts of the right lower lobe and basal parts of the medial and upper lobe on the same side; moreover, there was a general enlargement of the cardiac shadow to a maximum of 960 ml. (Fig. 3), corresponding to 560 ml. per square meter of body surface area (upper normal limit 400 ml./M.²). The electrocardiogram revealed low voltage, widespread T-wave inversion and a left-sided intraventricular conduction defect (see Fig. 2). With ACTH treatment, the patient recovered

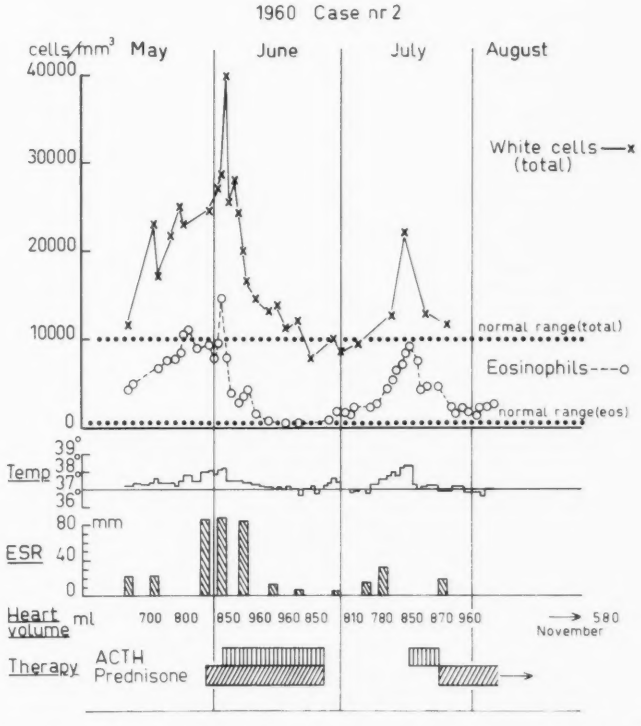

Fig. 4.—Diagram which shows white blood cell count, temperature (degrees C.), erythrocyte sedimentation rate (mm./hr.), total heart volume, and effect of therapy in Case 2.

gradually with a declining number of eosinophils, and the lung fields cleared on x-ray examination (Fig. 3). The electrocardiographic picture also improved with isoelectric and, later on, positive T waves. At the end of June an attempt was made to withdraw the ACTH and steroid treatment. This resulted in an immediate recurrence of all the previous symptoms with periods of supraventricular tachycardia of very high rate (220 per minute) and infiltrations of other parts of the lungs shown on chest x-ray examination, together with symptoms of bronchial obstructions and marked eosinophilia. The second course of ACTH and steroid medication was now started and this resulted in a dramatic decrease of all the symptoms, with a marked drop in temperature, pulse rate, and number of eosinophils. On discharge from the hospital the patient was symptom free except for a slight paresis of the extensor muscles of the right foot. Repeated examinations have revealed a persistent eosinophilia (1,000 per cubic millimeter) but a normalized heart volume. The patient is kept on long-term steroid treatment (10 mg. prednisone daily). Exercise tolerance test and spirometry are normal.

Laboratory Studies.—Essentially the same findings as in Case 1 apply here in regard to hemoglobin (12 to 14 Gm. per 100 ml.), serum proteins, and sternal marrow biopsy.

Sputum specimens were negative, as were urinalysis and serologic tests, liver function tests, L.E. cell tests and, stool examination for ova. Biopsy from lymph nodes, skin, and muscle did not shown any pathologic change.

CASE 3.—A woman, born in 1895, had no family history of allergic diseases. She was healthy until September, 1959, when symptoms of asthmatic bronchitis appeared. There had been no previous heart disease or symptoms of heart failure. In January, 1960, the patient was hospitalized for right-sided pneumonia, which responded favorably to antibiotics. A differential white cell count showed 7 per cent eosinophils at this time.

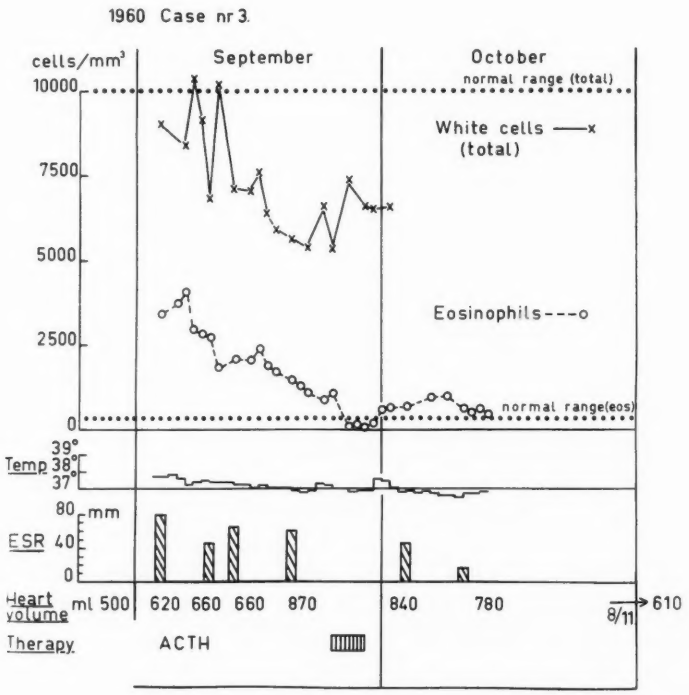

Fig. 5.—Diagram which shows white blood cell count, temperature (degrees C.), erythrocyte sedimentation rate (mm./hr.), total heart volume, and effect of therapy in Case 3.

The patient was readmitted in September, 1960, after a period of cough, increasing shortness of breath, and elevated temperature, which had not responded to antibiotics. On admission, the patient exhibited moderate symptoms of bronchial asthma. Physical examination revealed sonorous râles over both lung fields. Heart sounds were normal and without murmurs. Blood pressure was 150/85 mm. Hg. A roentgenogram of the chest, taken on the day of admission, showed confluent streaky infiltrations involving the lateral basal aspect of the left lung. The total count of eosinophils were markedly elevated (Fig. 5). An x-ray examination 4 days later showed almost complete absence of lung infiltrations. X-ray study of the sinuses gave evidence of chronic inflammatory changes. During hospitalization, serial electrocardiograms were obtained which initially were within normal limits. Subsequently widespread and pronounced T-wave inversions developed. Total heart volumes increased markedly (Fig. 5) during September but decreased later on. ACTH treatment resulted in considerable improvement in the patient's condition with a rapid fall in the number of eosinophils. Five days of treatment with 20 units per day was sufficient to bring about a lasting cure of the condition. On re-examination, the total eosinophil count has been normal. Spirometric pulmonary function tests and exercise tolerance test were normal.

Laboratory Studies.—Essentially the same findings as in Cases 1 and 2 also apply here. There was a slight rise of the globulin fraction of the serum proteins (2.1 to 2.6 Gm. per 100 ml., corresponding to 32 and 26 per cent of total proteins), but follow-up examination in January, 1961, showed normal values.

Table I gives the major clinical manifestations with reference to findings, which constitute evidence of cardiac involvement. The similarity of symptoms and signs in all patients is evident. Bronchial asthma and upper respiratory tract infections are the common clinical features in these patients, with an insidious onset of symptoms which lead to a stormy and protracted clinical course. Administration of corticotropin brought about a dramatic response and interrupted the unfavorable course of the disease.

TABLE I. SUMMARY OF CLINICAL MANIFESTATIONS

CASE NO.	MAJOR CLINICAL MANIFESTATIONS	EVIDENCE OF CARDIAC INVOLVEMENT
1	Bronchial asthma, sinus infection, eosinophilia, fever, transient pulmonary infiltration, elevation of ESR	S-T elevation and intraventricular conduction defect, marked tachycardia
2	Bronchial asthma, sinus infection, eosinophilia, fever, transient pulmonary infiltration, elevation of ESR	Cardiac enlargement, T inversion, intraventricular conduction defect, low voltage, marked sinus tachycardia, nodal tachycardia, systolic murmur
3	Bronchial asthma, sinus infection, eosinophilia, fever, transient pulmonary infiltration, elevation of ESR, slight hypergammaglobulinemia	Cardiac enlargement, T inversion, marked sinus tachycardia

REVIEW OF THE LITERATURE

Harkavy[8] was the first to give a comprehensive description of 16 patients with bronchial asthma which was accompanied by electrocardiographic abnormalities, blood eosinophilia, ranging from 7 to 84 per cent, as well as numerous manifestations in various organs. All patients presented the picture of migratory pulmonary infiltration, resembling the pulmonary lesions described by Loeffler. In 12 patients the electrocardiographic abnormalities disappeared with the subsidence of other symptoms but recurred with exacerbation. Pericarditis appeared in 4 patients and became chronic in 3 with signs of constrictive pericarditis. These 4 patients died and were available for necropsy studies. The cardiac lesions were characterized by chronic pancarditis with eosinophilic infiltration and arteritis in one patient with typical pericarditis nodosa. The author suggested bacterial allergy resulting from chronic sinus infections as the common causative etiology. The combination of these symptoms in cases of asthma has later been referred to as a clinical-pathologic entity, called "Harkavy's syndrome."

Churg and Strauss[2] described 13 cases (autopsy findings and biopsies) of allergic granulomatosis and vascular embarrassment in various organs. Three patients had cardiac involvement in combination with eosinophilia and pul-

monary infiltration. The cardiac lesions were described as granulomatous nodules in the pericardium and interstitial eosinophilic infiltrations. The basic anatomic changes in all cases consisted of widespread, vascular lesions of the type seen in periarteritis nodosa.

Ehrlich and Romanoff[5] presented the necropsy observations on a patient with bronchial asthma and eosinophilia, who died in status asthmaticus. Histologic studies revealed eosinophilic infiltration in the lungs and numerous other sites, including the pericardium, but there were no signs of arteritis.

Schwartz[15] published the report of a case of bronchial asthma accompanied by eosinophilia and multiple organ involvement. Clinically it was characterized by transitory pulmonary infiltration, blood eosinophilia, anemia, subcutaneous nodules, albuminuria, and acquired right bundle branch block. Biopsy of muscle tissue and subcutaneous nodule did not reveal histologic features characteristic of any recognized disease. Treatment with cortisone caused disappearance of clinical symptoms and there was a marked decrease in the number of eosinophils which increased again on the discontinuance of cortisone. Cortisone treatment, however, had no effect on the right bundle branch block.

Engfeldt and Zetterström[7] described the clinical and pathologic findings in 2 children with a systemic disease which exhibited characteristics related to Loeffler's syndrome and to periarteritis nodosa. The first patient died suddenly with symptoms of acute cardiac failure. Histologic examination of the heart disclosed pancarditis with focal muscle necrosis, eosinophilic infiltrations, and thrombotic obliteration of the nutrient vessels. The second patient recovered under the course of ACTH treatment. Biopsy from the skin, inguinal lymph nodes, and quadriceps muscle showed intense infiltration of eosinophilic leukocytes and endarteritic narrowing of the vessel lumina. The only sign of eventual cardiac involvement was transient enlargement of the heart. Pronounced hypergammaglobulinemia was present in both cases. The authors assumed that the clinical picture with a variety of systemic lesions was consistent with a state of hyperimmunization. They suggested the name "disseminated eosinophilic collagen diseases."

Leckert[9] reported a case of Loeffler's syndrome with clinical evidence of cardiac involvement (marked enlargement of the cardiac silhouette and transient S-T and T changes in the ECG). There was no history of allergy or bronchial asthma, but specimens of stool revealed infestation of Nematoda. A liver biopsy showed eosinophils in the sinusoids with normal architecture of the liver tissue and vessels. The patient made a complete recovery in a period of 5 months without therapy.

Pipkorn and Olsson[13] described a patient with a diagnosis of "myocarditis allergica." The predominant feature was eosinophilia and opacities on the chest roentgenogram together with symptoms of bronchial asthma. The patient died suddenly following cardiac arrest. Histologic examination showed necrotizing arteritis in the lung, heart, liver, and kidneys, with widespread eosinophilic infiltrations and "wire-loop" changes in the glomeruli. In the myocardium,

necrotic areas could be detected close to obliterated smaller arteries. Changes characteristic of periarteritis nodosa and even some features of disseminated lupus erythematosus and rheumatic granulomas were evident.

COMMENTS

A review of the literature revealed some patients with a similar clinical picture and histologic proof (postmortem or biopsy specimens) of pathologic changes in the myocardium, epicardium, and arteries. In the light of these observations it seems justified to present our cases as examples of eosinophilia with multiple organ involvement, including the heart. Evidence of cardiac disease in our patients is based on (1) tachycardia which cannot be explained by the degree of temperature elevation, (2) enlargement of the cardiac outlines (Cases 2 and 3) related to cardiac dilatation (pericardial effusion may have contributed to this finding but can hardly be regarded the sole cause), (3) transient systolic murmur (Case 2), possibly due to relative mitral insufficiency and (4) electrocardiographic changes consistent with perimyocarditis.

It is remarkable that in Case 2 the fulminating clinical picture developed under the course of prednisone medication. Treatment with ACTH, however, was effective and was followed by an immediate response.

Our patients present some features resembling periarteritis nodosa. Biopsy studies, however, failed to reveal a histologic picture, indicating necrotizing phlebitis. It is known, that these lesions may not be uniformly distributed throughout the vascular tree, and the small amount of tissue removed for biopsy may not be representative of the whole vascular system. Case 2 was particularly suggestive of periarteritis nodosa because of the symptoms of polyneuritis, which is not an uncommon finding in this disease. According to Talbot and Ferrandis[16] approximately 50 per cent of the patients with periarteritis nodosa exhibit signs or symptoms of peripheral neuritis, which are looked upon as manifestations of vascular lesions of the vasa nervorum, according to Lovshin and Kernohan.[11] Divertie and Olsen,[4] in a comparative study of Loeffler's syndrome and periarteritis nodosa, noticed a marked eosinophilia in about one fourth of the cases of periarteritis nodosa. However, the incidence of combined pulmonary infiltration and blood eosinophilia, associated with periarteritis nodosa, was only about 10 per cent. These authors considered the presence of an anemia and impaired renal function to be diagnostic of periarteritis nodosa, these signs being usually lacking in Loeffler's syndrome. Moreover they were of the opinion that a history of bronchial asthma extending over several years is typical of Loeffler's syndrome.

Whether our cases should be considered to be a variety of Loeffler's syndrome is entirely a matter of definition. Generally, however, this term is reserved for patients with a mild, abortive clinical course. Our cases most closely resemble Harkavy's syndrome, that is—pulmonary infiltration with blood eosinophilia in cases of bronchial asthma and cardiac involvement.

The incidence of bronchial asthma and marked blood eosinophilia have led to the suggestion that hypersensitivity plays a part in its pathogenesis. Harkavy[5]

established the hypothesis of vascular allergy, due to a hypersensitivity reaction to chronic bacterial infections. In fact in all our cases there was evidence of sinus and respiratory tract infections.

The presumption of a hypersensitivity reaction and evidence of multiple organ involvement in our patients should raise the question as to whether the various signs are facets of a systemic disease, such as a collagen disorder. Hyperimmune reactions with the production of abnormal antibodies and eosinophilia are considered to be of etiologic importance in maladies of this kind. These are characterized by hypergammaglobulinemia, which was present only in Case 3. Wood,[17] with the experience of some similar cases, classified them as instances of collagen disease.

SUMMARY

The clinical findings of 3 cases of marked eosinophilia, transitory pulmonary infiltrations, and cardiac involvement are reported. The disease was characterized by a protracted and severe clinical course which could be interrupted by ACTH treatment followed by long-term steroid therapy. The pertinent literature on similar cases is reviewed and the etiology discussed.

We wish to thank Lars Olof Lanner, M.D., from the Roentgen Department II, Sahlgrenska Sjukhuset, Göteborg, for helping us to evaluate the roentgenograms.

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A COMPARISON OF VARIOUS EXPECTORANT DRUGS EMPLOYING A NEW METHOD FOR DETERMINING SPUTUM VISCOSITY

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THERE has always been a great amount of argument about the "viscosity" of sputum and the effect of certain drugs on this particular symptom. According to Dorland,[4] a viscous sputum is one which is sticky, gummy, clammy, or glutinous. Nothing is said about the sputum being thick, yet the physician's aim is to "thin" it by using expectorant drugs. Again, according to Dorland,[4] an expectorant "promotes the ejection by spitting of mucous or other fluids from the lungs, bronchi, and trachea." One may assume that the sputum would be more easily raised if it was more fluid, but would this be true also if the sputum was viscous or sticky?

Rather than become involved in semantics, we will use terms as they are employed by fellow physicians. Drugs which "thin" sputum thus make it less viscid and easier for the patient to raise (expectorant action). We studied more commonly used medicinals for this purpose, namely, potassium iodide and ammonium chloride. Since there was a question as to whether trypsin and chymotrypsin taken orally also act in this way, Chymoral tablets were added to the study.

Still not knowing exactly what we wanted to measure, the closest term seemed to be "viscosity" and, therefore, a viscometer was used which gives a reading for the sputum specimen relative to that for water.

PATIENTS

The patients included in this series were mostly World War I veterans, all male, with chronic lung disease (nontuberculous) and carrying such diagnoses as: chronic bronchitis, asthmatic bronchitis, pulmonary emphysema, and bronchial asthma. They presented all the signs and symptoms of intractable asthma and chronic obstructive pulmonary disease. All complained of difficult production of thick, mucoid sputum.

The patients ranged in age from 47 to 72 years, the average being 59. All had been receiving bronchodilators but no iodides or other expectorant drugs for at least one week before the beginning of the study. Most of them complained of shortness of breath and wheezing on mild exertion or change of position, partially relieved by productive cough. There appeared to be no

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seasonal or geographical influence; however, damp weather or acute upper respiratory infection did, in most instances, augment the severity of the condition. Symptoms were generally worse on arising in the morning. In none was there a clear-cut personal or family allergic history. All had been under observation from 1 to 5 years and were receiving maintenance doses of bacterial vaccines or filtrates.

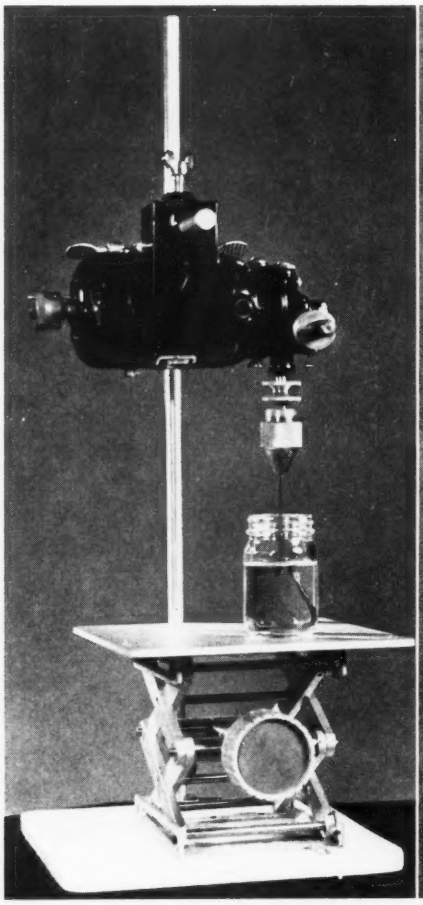

Fig. 1.

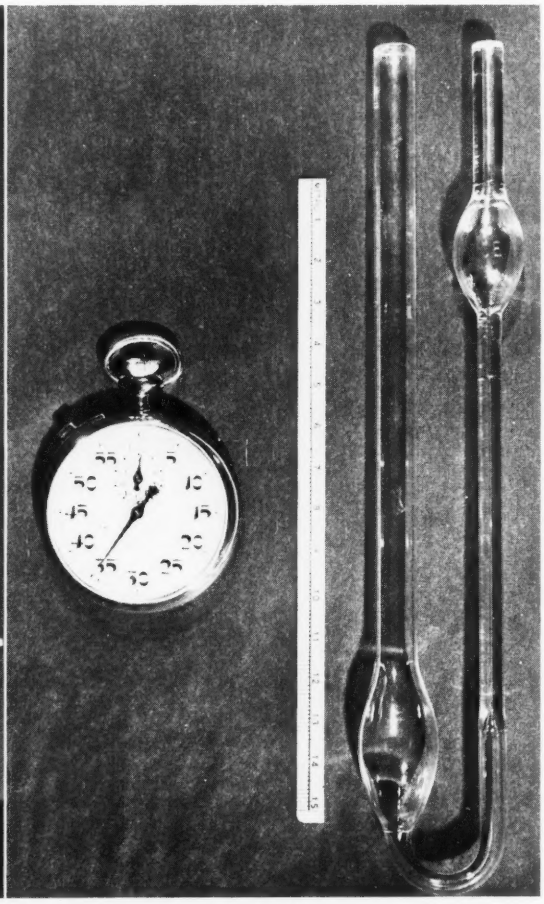

Fig. 2

Fig. 1.—Variable speed blending apparatus used to blend the sputum specimen prior to determining its relative viscosity.

Fig. 2.—Ostwald viscometer and stop watch used to determine sputum relative viscosity at 37° C.

DRUGS

All patients received all three drugs in the same order, but the first drug given was randomized so that approximately the same number were started on each. Control and drug administration periods were each one week in length. Therefore, there were four control periods—preceding and following the study and between the weeks when the drugs were administered.

The drugs given for a period of one week were:

1. Saturated solution of potassium iodide—10 drops in water three times daily, after meals. Each dose of 10 drops contained 400 mg. of potassium iodide.

2. Chymoral tablets*—given four times a day (after meals and at bedtime). Each tablet provided enzymatic activity equivalent to 50,000 Armour Units, supplied by a purified concentrate which had specific trypsin and chymotrypsin activity in a ratio of approximately six to one.

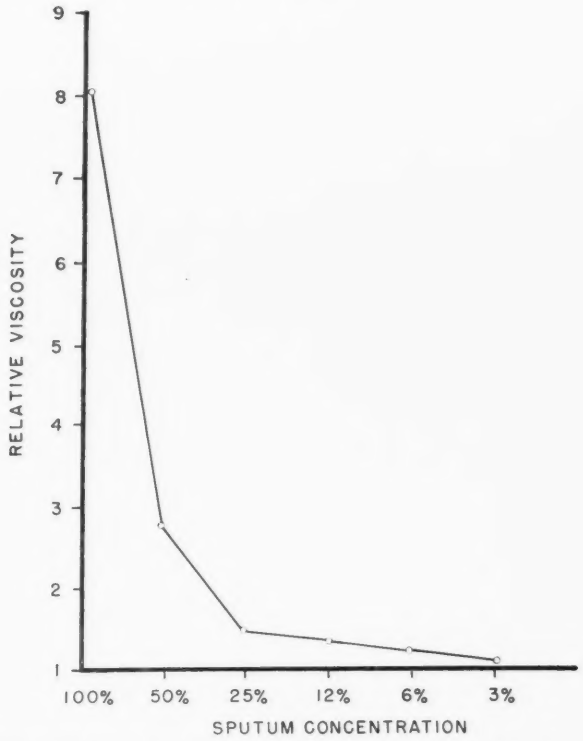

Fig. 3.—Standard curve for transposing diluted sputum values to undiluted.

3. Ammonium chloride—500 mg. four times daily (after meals and at bedtime) dissolved in a mixture of glycerine, fluid extract of Glycyrrhiza, lemon flavor, syrup, and distilled water.

METHOD

Twenty-four hour sputum specimens were collected at the end of each week of treatment or nontreatment (referred to as control). The volume of each specimen was determined and its appearance noted. The impressions of the patient as to volume, change in consistency, and ease of production were also recorded. The sputum specimens were blended by vigorously stirring for 6 minutes at a constant speed in the apparatus shown in Fig. 1. The relative

*Furnished through the courtesy of Armour Pharmaceutical Company, Kankakee, Ill.

viscosity of the sputum was then measured at 37° C. in an Ostwald viscometer (Fig. 2) by comparing the rate of flow of the sputum samples with that of water. If the sputum flow was inordinately slow, the specimen was mixed with an equal volume of distilled water and again stirred for 6 minutes. This dilution process was repeated until a reasonable flow time was obtained. A standard curve was prepared from those specimens that could be measured at six serial dilutions as shown in Fig. 3. The relative viscosity indices of the diluted specimens were extrapolated from this curve to a zero dilution value. Table I was prepared to facilitate transposing diluted to undiluted relative viscosity values.

TABLE I. TRANSPOSITION TABLE FOR DETERMINING SPUTUM VISCOSITY VALUES

MEASURED VALUE	SPUTUM DILUTION MEASURED				
	50%	25%	12%	6%	3%
1	6.25	7.50	7.80	7.95	8.05
2	7.25	8.50	8.80	8.95	9.05
3	8.25	9.50	9.80	9.95	10.05
4	9.25	10.50	10.80	10.95	11.05
5	10.25	11.50	11.80	11.95	12.05
6	11.25	12.50	12.80	12.95	13.05
7	12.25	13.50	13.80	13.95	14.05
8	13.25	14.50	14.80	14.95	15.05
9	14.25	15.50	15.80	15.95	16.05
10	15.25	16.50	16.80	16.95	17.05
15	20.25	21.50	21.80	21.95	22.05
20	25.25	26.50	26.80	26.95	27.05
25	30.25	31.50	31.80	31.95	32.05
30	35.25	36.50	36.80	36.95	37.05
35	40.25	41.50	41.80	41.95	42.05
40	45.25	46.50	46.80	46.95	47.05
45	50.25	51.50	51.80	51.95	52.05

RESULTS

Tables II, III, and IV give the sputum viscosity indices for the control and treatment periods of the three groups of patients, divided according to the initial drug given.

TABLE II. SPUTUM RELATIVE VISCOSITY INDICES OF GROUP I SUBJECTS (POTASSIUM IODIDE INITIALLY)

SUBJECT NUMBER	CONTROL PERIOD I	IODIDE TREATMENT	CONTROL PERIOD II	CHYMORAL TREATMENT	CONTROL PERIOD III	AMMONIUM CHLORIDE TREATMENT	CONTROL PERIOD IV	MEAN CONTROL VALUE
1	8.4	8.4	9.5	21.8	11.4	10.5	11.3	10.2
2	12.1	23.8	13.2	47.8	17.3	19.8	15.0	16.9
5	8.3	12.4	13.1	12.0	15.7	17.2	12.0	12.3
11	22.1	16.8	12.1	27.6	12.1	20.9	11.1	14.4
14	6.8	6.5	16.8	2.5	3.9	9.6	4.1	7.9
15	14.9	10.2	11.7	10.1	8.2	9.4	22.4	14.3
19	10.8	9.8	9.8	9.8	10.7	9.6	18.2	12.4
26	8.7	9.7	8.9	11.0	19.1	10.3	11.1	12.0

Tables V and VI summarize the changes in viscosity (increase or decrease) from control to treatment and from treatment to control periods, respectively, for each of the drugs used. It can be seen that there is no specific trend in the sputum viscosity from control to treatment or treatment to control periods.

TABLE III. SPUTUM RELATIVE VISCOSITY INDICES OF GROUP II SUBJECTS (CHYMORAL INITIALLY)

SUBJECT NUMBER	CONTROL PERIOD I	CHYMORAL TREATMENT	CONTROL PERIOD II	AMMONIUM CHLORIDE TREATMENT	CONTROL PERIOD III	IODIDE TREATMENT	CONTROL PERIOD IV	MEAN CONTROL VALUE
4	14.3	10.6	10.3	14.7	12.0	12.6	15.9	13.1
6	9.2	9.8	7.2	3.0	2.8	8.8	8.4	9.2
8	8.1	11.8	14.1	9.7	7.5	8.7	8.7	9.6
13	9.5	8.7	10.7	13.3	10.9	11.4	18.3	12.4
17	8.9	9.1	8.6	9.8	7.8	7.2	8.4	8.4
18	10.4	2.4	6.7	1.2	6.3	8.2	1.1	6.1
20	7.9	8.7	8.7	7.7	13.5	24.3	11.6	10.4
23	8.2	13.6	10.6	11.0	9.5	10.4	10.7	9.8
24	8.6	7.9	7.9	8.0	13.2	7.7	6.7	9.1
25	16.7	5.5	11.0	7.7	8.4	7.8	10.2	11.6

TABLE IV. SPUTUM RELATIVE VISCOSITY INDICES OF GROUP III SUBJECTS (AMMONIUM CHLORIDE INITIALLY)

SUBJECT NUMBER	CONTROL PERIOD I	AMMONIUM CHLORIDE TREATMENT	CONTROL PERIOD II	IODIDE TREATMENT	CONTROL PERIOD III	CHYMORAL TREATMENT	CONTROL PERIOD IV	MEAN CONTROL VALUE
3	21.0	8.9	21.9	11.6	10.6	10.9	9.4	15.7
7	15.3	11.9	11.6	10.1	7.8	11.2	9.2	11.0
9	9.1	8.6	4.2	7.5	7.8	6.1	7.4	7.1
10	11.5	9.6	12.3	14.0	19.9	8.6	9.9	13.4
12	8.4	13.6	10.2	11.1	13.8	22.5	12.8	11.3
16	18.9	8.8	9.8	10.4	7.7	10.3	7.6	11.0
21	11.2	8.3	15.1	10.0	16.7	7.7	9.1	13.0
22	10.0	14.5	59.3	10.5	31.7	17.5	12.3	28.3
27	8.4	7.9	5.7	7.8	7.4	10.1	7.6	7.3

TABLE V. CHANGES IN SPUTUM VISCOSITY FROM CONTROL TO TREATMENT PERIODS

DRUG	LESS VISCOUS	MORE VISCOUS	NO CHANGE
Chymoral	12	14	1
Potassium iodide	11	15	1
Ammonium chloride	15	11	1

TABLE VI. CHANGES IN SPUTUM VISCOSITY FROM TREATMENT TO CONTROL PERIOD

DRUG	LESS VISCOUS	MORE VISCOUS	NO CHANGE
Chymoral	14	11	2
Potassium iodide	12	13	2
Ammonium chloride	13	12	2

Since others[2, 5] have shown a marked variation in the sputum viscosity of an individual subject, the relative viscosity of the subject's sputum following treatment was compared with the mean relative viscosity value obtained from the four control periods, to correct for a possible fluctuating baseline. Table VII shows that there was a trend for all of the drugs used to lessen the viscosity of the sputum, with potassium iodide being slightly more effective than Chymoral and both more effective than ammonium chloride.

TABLE VII. EFFECT OF TREATMENT ON SPUTUM VISCOSITY*

DRUG	LESS VISCOUS	MORE VISCOUS	NO CHANGE
Chymoral	16	9	2
Potassium iodide	17	8	2
Ammonium chloride	13	12	2

*Viscosity values compared with the average of the four control periods regardless of which drug was used initially. Changes of less than 0.5 relative viscosity units were considered no change.

A comparison of the patients' impressions of changes in sputum volume and viscosity against measured values showed a marked lack of correlation. Table VIII shows how reliable the patients' estimations really were and Table IX indicates the actual change in measured volume of sputum for 24 hours from control to medication.

TABLE VIII. SUBJECTS ESTIMATION VERSUS ACTUAL SPUTUM PRODUCTION AND CHANGE IN VISCOSITY

VOLUME ESTIMATE			CHANGE IN VISCOSITY ESTIMATE	
RELIABLE*	UNDER	OVER	AGREE†	DISAGREE
84	18	84	31	131

*Reliable—within 0.5 ounces of actual volume.

†Agreement on viscosity—whether sputum was thicker, thinner, or the same as previously noted.

TABLE IX. CHANGE IN MEASURED VOLUME OF SPUTUM ON DRUGS USED

	POTASSIUM IODIDE	CHYMORAL	AMMONIUM CHLORIDE
Increased amount	11	9	10
Decreased amount	15	13	13
Same amount	1	5	4

DISCUSSION

In reviewing the literature, the first mention of a viscometer was by Basch, Holinger, and Poncher[1] in 1941. They used a narrow glass tube and measured sputum flow under pressure, but others employing the same method could not obtain repeatable results with the same specimen of sputum. Blanchard[2] describes the measurement of sputum viscosity using a torque viscometer. While this apparatus is fairly accurate considering the inhomogeneity of sputum, its cost ($3,000 to $4,000) prohibits its use in the average hospital. For this reason, we decided to explore a cheaper and simpler method.

The blending apparatus as pictured in Fig. 1 was assembled from materials available in the laboratory. Any like mixer such as the Hamilton or Waring Blendor could be used when operated at a moderate but constant speed. Preliminary studies using our apparatus for various lengths of time demonstrated that in 6 minutes the maximum amount of blending could be accomplished.

If the viscosities of all sputum specimens could be determined without dilution, this would be a simpler and more desirable procedure. By blending, an average viscosity of the entire specimen is obtained and the bore is not obstructed by plugs, such as the pearls of Laennec or Curschmann's spirals. Increasing

the bore of the viscometer to accommodate more viscous sputa would decrease the flow time of less viscous sputa to such an extent that differences in flow time would be so small as to be indistinguishable.

There might be some question as to the effect of saliva or other secretions diluting the sputum specimen. If differences were reflections of varying amounts of secretions in the "true sputum," there should be an inverse relationship between differences in sputum volume and viscosity. When data from this study were examined for such an inverse relationship, none were found. Specimens showing little or no change in volume or viscosity were not scored. Of the remaining samples, seventy-three direct relationships between viscosity and volume were noted and sixty-three specimens exhibited an inverse relationship. Since only trends were recorded and the degree of change was not considered, the apparent direct relationship is indicative that salivary contamination has little or no effect on relative viscosity measurements. Forbes and Wise[5] also report that wide variations in sputum viscosity were independent of sputum volume.

The efficacy of expectorant drugs is apparently more of an art than a science and for this reason has always been a matter of controversy. Several authors[5, 6] have published reports on the lack of objective change in sputum viscosity using potassium iodide, ammonium chloride, or nebulized trypsin. Others[3, 7, 8] state that these expectorant drugs do decrease the viscosity of sputum and increase its volume but no objective proof is offered. The unreliability of patients' reports is particularly noticeable in the lack of correlation in our series between patients' statements and the actual measurements on the same sputa.

In the patients studied, all of the drugs reduced the relative viscosity below the mean control level—with potassium iodide and Chymoral somewhat more effective in this respect than ammonium chloride. However, these results are not statistically significant. In many instances, one drug was more effective for a particular patient than either of the other two. Frequently patients felt clinically improved on expectorants, although measurements disclosed little or no change in volume, viscosity, or appearance of their sputa. Therefore, the drug of choice to be used for a given patient can be determined only by trial.

Should a good expectorant drug increase or decrease the volume of sputum? It is our belief that the volume should be increased. However, the volumes were decreased more than increased and these changes are not considered to be significant with this small number of patients.

We feel that the dosage of both potassium iodide and ammonium chloride were adequate. Possibly Chymoral would have exhibited a greater effect if used in double our dosage as employed by Taub.[5]

SUMMARY AND CONCLUSIONS

A new inexpensive method of easily estimating the viscosity of sputum has been presented. Using this method, little change was noted between the control weeks and the periods when these patients with chronic obstructive pulmonary

disease were taking potassium iodide, Chymoral tablets, or ammonium chloride. It is possible, however, that we are dealing with random variations in sputum viscosities and that none of the drugs was effective.

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EXPERIMENTAL EOSINOPHILIA: LOCAL TISSUE REACTION TO ASCARIS EXTRACTS

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THE EOSINOPHIL has a remarkably frequent, if not constant, association with the breakdown of protein. In the antigen-antibody reaction there is an accumulation of protein end products, some with far-reaching physiologic and pathologic potential.[1, 2] Injections of polypeptides derived from parasitic worms, particularly Ascaris, can produce anaphylactoid reactions and eosinophilia in experimental animals, effects probably unrelated to the antigen-antibody reaction as they can be produced upon single injection. Attempts to isolate substances which can evoke experimental eosinophilia have usually yielded mixtures of unidentified polypeptides, polysaccharides, or their catabolic products, among which histamine is repeatedly mentioned.[3-9]

In two previous studies[9, 10] water soluble polypeptides and polysaccharides derived from Ascaris were injected into the peritoneal cavity of guinea pigs. Readily absorbed, these materials appeared to excite little local tissue reaction but did produce interesting changes in remote tissues and organs which were regarded as part of the later phase of eosinophil activity. Insoluble Ascaris derivatives have excited local reactions,[4] and, to facilitate study of the earlier phases of eosinophil activity, insoluble Ascaris materials were prepared and injected into the subcutaneous tissues of the guinea pig. The ensuing histologic changes and their probable relationship to the function of the eosinophil are presented here.

MATERIALS, ANIMALS, AND METHODS

Ascaris Extracts.—Washed *Ascaris lumbricoides* var. *suum,* obtained from slaughtered hogs, were pulped in a tissue blender in an equal volume of 10 per cent trichloracetic acid, the resulting fluid quickly settling to a pink sediment with white supernatant. Polysaccharide was extracted from the supernatant as described elsewhere,[9] while the sediment was washed in water, adjusted to pH 7.2, passed through ethanols and ether, and finally dried at room temperature. This was a gray-green granular material which when wet resembled the grumous contents of an epidermoid cyst. Both polysaccharide and protein rich material were sterilized by heating to 56° C. for 20 minutes on 3 successive

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days; check cultures in thioglycollate broth were sterile at 72 hours' incubation. These materials, stored at –20° C., were used within 4 weeks of preparation.

Animals.—Baby guinea pigs were separated from the mother at 7 days and tests were started before they were 4 weeks old; all weighed less than 200 grams. The diet was a standard pellet chow supplemented by fresh vegetables thrice weekly. Materials were inserted into the subcutaneous tissues through small wounds in the skin of the back, two implants being made in each animal, one sealed with collodion and the other left uncovered. This latter was induced at intervals to exude fluid by gently squeezing the tissues; smears were made of the exudate using a technique similar to that of Kolouch.[11] The method of Rebuck and his co-workers,[12] in which coverglasses are placed over the wound and removed at intervals, was unsuccessful because of loss, breakage, and spoilage of the specimens by the animals. Blood samples were taken from a freshly nicked ear and animals were killed by exposure to chloroform vapor, autopsied at once, and appropriate specimens were taken for histologic and hematologic study.

Methods.—Standard techniques were used for eosinophil and total leukocyte counts. Smears were made on slides, blood being spread by a coverglass pulled sideways, so combining the advantage of more uniform distribution of cells in the coverglass method[13] with the ease of staining slides. Stains used for blood smears were Wright and Giemsa, and for tissues were hematoxylin-eosin, trichrome, and Giemsa.

Because of the many inherent errors in counting blood cells (even by practiced technique), direct and indirect counts of eosinophils frequently failed to agree, but the difference was seldom greater than ±20 per cent. All eosinophil counts in the tables are expressed to the nearest ten cells per cubic millimeter, a degree of significance adequate for this study. In assessing other leukocyte changes, all white cells were computed in absolute numbers from total count and smear ratios; no comparisons were made on percentages alone. These data proved to be voluminous and, as they added little to this presentation, they are not reported here. Histologically there was little difference between sealed and open lesions. To avoid repetitive and possibly confusing detail, the lesions have not been described individually. Instead, a collective assessment of lesions in chronological sequence is given.

PROCEDURE

Experiment 1.—

Each of 15 guinea pigs received two subcutaneous implantations of Ascaris polysaccharide (0.25 mg.), one wound being sealed and the other left uncovered. In the ensuing 72 hours, samples of peripheral blood and exudate from the uncovered wound were taken at intervals. The animals were killed at 1, 2, 3, 6, 9, 12, 15, 24, 48, and 72 hours and autopsied. Control peripheral blood studies were made on guinea pigs subjected to incision without implantation.

Blood changes: Nine animals showed a mild increase in neutrophils which appeared 2 hours after implantation, reached a peak of 10,000 to 12,000 leukocytes per cubic millimeter at about 12 hours, and subsided to normal levels at 24 hours. There was a simultaneous fall in lymphocytes to low normal values, with a return to initial levels at 24 hours. With the exception of animals killed before 3 hours, all showed a distinct eosinophilia (Table I) maximal at 12 or 24 hours and subsiding at 48 hours. Monocytes showed no consistent trend and no change in basophils was noted. Control studies were unremarkable.

TABLE I. EOSINOPHIL LEVELS IN NORMAL UNSENSITIZED GUINEA PIGS GIVEN SUBCUTANEOUS IMPLANTS OF ASCARIS POLYSACCHARIDE, EXPRESSED AS CELLS PER CUBIC MILLIMETER OF BLOOD

		HOURS								
	INITIAL	1	2	3	6	12	24	36	48	72
1	250	240	–	–	–	–	–	–	–	–
2	90	180	–	–	–	–	–	–	–	–
3	230	–	590	–	–	–	–	–	–	–
4	170	–	270	–	–	–	–	–	–	–
5	110	270	520	1,830	–	–	–	–	–	–
6	120	100	290	720	–	–	–	–	–	–
7	30	–	–	180	500	–	–	–	–	–
8	390	–	–	420	490	–	–	–	–	–
9	120	–	–	–	400	1,120	–	–	–	–
10	180	–	–	–	890	780	–	–	–	–
11	60	–	220	–	1,100	1,600	2,200	–	–	–
12	220	–	250	500	610	720	780	–	–	–
13	170	–	–	–	960	–	1,910	1,200	–	–
14	210	–	–	600	–	420	350	–	270	–
15	130	–	–	250	–	450	270	–	260	180
Control	190	60	–	180	0	70	110	–	200	180
Control	120	–	60	–	80	150	210	–	120	160

Legend: The symbol—indicates that no count was made.

Exudates: Early smears contained only cellular debris and a few red cells but at 3 hours became more cellular with granulocytes and monocytes prominent. In succeeding smears, granulocytes increased steadily in numbers with a left nuclear shift, while monocytes became less conspicuous and later disappeared. Eosinophils were scanty and no basophils, lymphocytes, or plasma cells were seen; occasional histiocytes appeared in late smears. Smears of exudate taken at 24 hours yielded little cellular material and were discarded.

Skin lesions: Sealed and open lesions differed little, and all sections included a small epidermal wound extending into the upper dermis. In the earliest lesions, this wound contained red blood cells, fibrin, and a few leukocytes but neither polysaccharide nor any significant open spaces were found. At 3 hours, hyperemia of local capillaries and leukocytic margination with emigration were observed, the cells being neutrophils and monocytes. In later sections the neutrophilic infiltration increased steadily up to 24 hours after which it became noticeably less dense. Eosinophils were not prominent, lymphocytes were infrequent, and no mast cells or plasma cells were encountered. After 24 hours, histiocytes appeared with increasing frequency and, later still, fibroblasts and

early fibrosis were seen. In summary, implanted material disappeared rapidly and mild infiltration by neutrophils occurred with the institution of a natural healing process.

Experiment 2.—

Each of 18 guinea pigs received two subcutaneous implantations of insoluble Ascaris protein (25 mg.), one wound being sealed and the other left uncovered. Samples of peripheral blood and wound exudate were taken as before and the animals were killed and autopsied at the same intervals.

Blood changes: Fifteen animals showed a transient neutrophilia with mild depression of lymphocytes as in the first experiments, peaks and normal values being recorded at similar times. All but 2 animals showed increased eosinophils (Table II), 8 animals registering abnormal levels; initial values were regained at 24 to 48 hours. Monocytes were inconsistent and no changes in basophils were noted.

TABLE II. EOSINOPHIL LEVELS OF NORMAL UNSENSITIZED GUINEA PIGS GIVEN SUBCUTANEOUS IMPLANTATIONS OF ASCARIS PROTEIN, EXPRESSED AS CELLS PER CUBIC MILLIMETER OF BLOOD

		HOURS								
	INITIAL	1	2	3	6	9	12	24	48	72
1	10	400	310	–	–	–	–	–	–	–
2	10	380	560	–	–	–	–	–	–	–
3	120	50	60	–	–	–	–	–	–	–
4	80	100	190	240	–	–	–	–	–	–
5	130	300	210	790	–	–	–	–	–	–
6	0	220	220	330	–	–	–	–	–	–
7	390	–	–	510	770	–	–	–	–	–
8	370	–	–	480	800	–	–	–	–	–
9	210	–	–	450	280	–	–	–	–	–
10	170	–	200	–	240	580	–	–	–	–
11	400	–	420	–	360	660	–	–	–	–
12	230	–	–	–	490	–	210	–	–	–
13	260	–	–	–	390	–	130	–	–	–
14	80	–	–	–	280	–	320	110	–	–
15	0	–	–	–	120	–	300	310	–	–
16	170	–	–	–	180	–	240	70	–	–
17	50	–	–	170	370	–	–	320	110	–
18	80	–	–	290	510	–	–	470	190	–

Legend: The symbol — indicates that no count was made.

Exudates: Smears became cellular at about 3 hours, monocytes and neutrophils being the most frequent leukocytes although lymphocytes were also seen. Some lymphocytes contained basophilic cytoplasmic granules whereas others had a diffuse cytoplasmic basophilia reminiscent of plasma cells. A few monocytes also contained granular cytoplasmic inclusions. As the granulocytic reaction increased, monocytes and lymphocytes became less conspicuous; with few exceptions eosinophils were not seen before 6 hours and were seldom prominent in the smears. At 24 hours, nearly all cells were neutrophils although occasional histiocytes, sometimes with cytoplasmic inclusions, began to appear at this time. No basophils were seen.

Skin lesions: Sealed and open lesions again showed little difference, and each section included a small epidermal wound extending into the upper dermis.

In all sections this wound contained red cells, fibrin, and easily recognized fragments of Ascaris protein, including ova. Little cellular reaction was detected before 3 hours, when, in the tissue adjacent to the wound, dilated capillaries were noted with margination and emigration of mature neutrophils, monocytes, and rare eosinophils. At 6 hours, the tissue was loosely infiltrated by leukocytes, mostly neutrophils, and the protein implant invested by a thin rim of similar cells. Later, when the layer of investing leukocytes was much thicker, the implant now bore an irregular and scalloped outline (Fig. 1). At the same time many of the neutrophils contained dark cytoplasmic granules

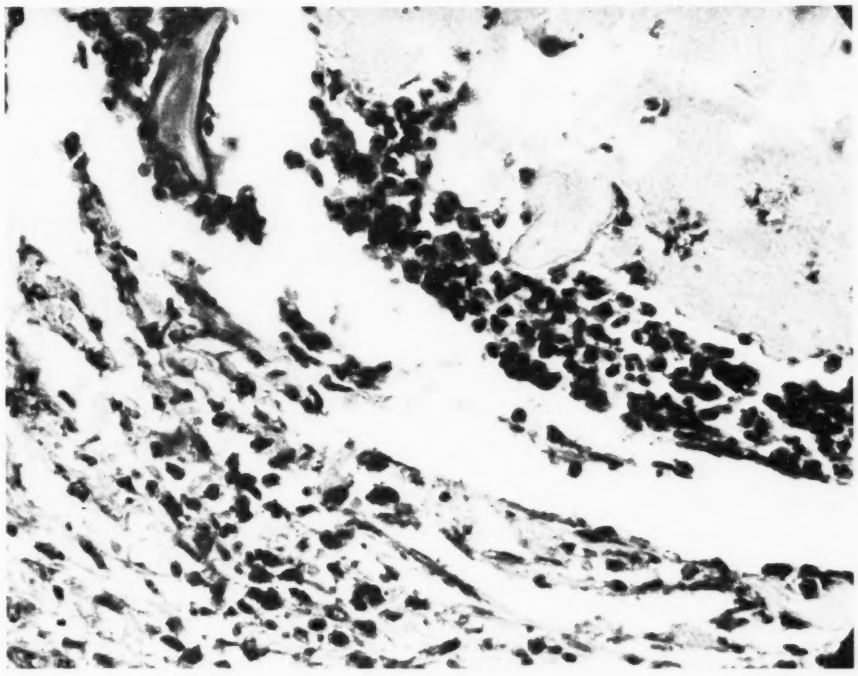

Fig. 1.—Ascaris protein implant invested by layers of phagocytic leukocytes and showing an irregular scalloped outline. Cells closest to the implant are mostly neutrophils. Eosinophils are most frequent in the outer edge of this layer and in the loose connective tissue behind. This is from a 12-hour lesion in an unsensitized guinea pig (Exper. 2). (Hematoxylin and eosin, × 720; reduced ⅔.)

while others were frankly degenerate, frequently associated with large mononuclear phagocytes. Eosinophils began to appear prominent at 12 hours and, while a few lay close to the protein, most were found behind the neutrophils and in advance of the loose accumulation of histiocytes that appeared at about 24 hours. There was no sign of vascular emigration of histiocytes; instead there were many examples of local histiocyte formation in the tissues deep to the wound. Here many capillaries and small arterioles had thickened walls composed of layers of mononuclear cells extending outward, forming a collar. Some outer cells were only tenuously attached to the vascular proliferation, whereas many identical cells lay free in the perivascular tissue. These were indistinguishable from tissue histiocytes (Fig. 2). As active emigration of neutrophil

Fig. 2.—*A*, proliferation of capillary wall with formation of hystiocytic elements in 48-hour lesion in unsensitized guinea pig (Exper. 2). (Hematoxylin and eosin, × 900; reduced ⅔.)

B, Proliferation of arteriolar wall and extension of reaction into perivascular tissues forming a collar of mononuclear cells. When lying free in the tissues, these are indistinguishable from tissue histiocytes. A few eosinophils lie in the perineural lymphatics. This is from a 72-hour lesion in a sensitized guinea pig (Exper. 3). (Hematoxylin and eosin, × 250; reduced ⅔.)

leukocytes slackened pace at about 36 hours, the area of cellular infiltration gradually became more circumscribed and now a familiar pattern emerged. A central area contained Ascaris protein remnants and large numbers of neutrophil granulocytes, metamyelocytes, and even myelocytes, many being degenerate and frankly necrotic. This central zone was surrounded by a wide band of histiocytes, some more central cells actively phagocytosing adjacent cellular debris; occasional bi-nucleate forms were seen. Eosinophils were sprinkled throughout the lesion, often close to the histiocytes but no phagocytosis of eosinophils was observed. Eosinophils were also seen in the outer loose connective tissue, frequently lying within dilated lymphatics of the dermal papillae or in the deep perineural lymphatics (Fig. 3). No mast cells were seen. In summary, this lesion showed moderate neutrophil infiltration and partial destruction of the foreign protein with necrosis of the neutrophils; there was accumulation of eosinophils and a well-marked histiocytic response with the eventual formation of a circumscribed foreign body granuloma.

TABLE III. EOSINOPHIL LEVELS IN SENSITIZED GUINEA PIGS FOLLOWING A SECOND SUBCUTANEOUS IMPLANTATION OF ASCARIS PROTEIN, EXPRESSED AS CELLS PER CUBIC MILLIMETER OF BLOOD

	BEFORE SENSITIZATION	BEFORE CHALLENGE	HOURS								DAYS
			1	2	3	6	12	24	48	72	6
1	140	180	210	120	300	–	–	–	–	–	–
2	80	70	480	450	310	–	–	–	–	–	–
3	200	110	120	120	240	–	–	–	–	–	–
4	290	160	–	–	300	490	–	–	–	–	–
5	30	120	–	–	40	210	–	–	–	–	–
6	80	90	–	–	110	70	–	–	–	–	–
7	140	120	–	–	210	330	400	–	–	–	–
8	160	80	–	–	60	280	320	–	–	–	–
9	260	190	–	–	290	400	410	–	–	–	–
10	180	100	180	140	290	500	390	200	–	–	–
11	100	90	280	300	300	320	290	390	–	–	–
12	220	100	–	–	–	520	570	410	–	–	–
13	120	100	–	450	420	420	–	330	390	–	–
14	150	80	–	–	–	330	–	410	360	–	–
15	80	40	–	–	–	240	400	180	220	190	–
16	10	120	–	–	–	180	510	160	120	240	–
17	120	20	–	–	–	190	220	440	300	120	170
18	180	100	–	–	330	450	510	660	190	170	190

Legend: The symbol — indicates that no count was made.

Experiment 3.—

Each of 18 guinea pigs received two subcutaneous implantations of insoluble Ascaris protein (25 mg.), both wounds being sealed. Six weeks later this operation was repeated and this time one wound was sealed and the other left uncovered. After the first implantation, no blood or exudate studies were undertaken, but after the second implantation, samples of peripheral blood and exudate were taken as before. The animals were killed at 3, 6, 12, 24, 48, and 72 hours and, also, at 6 days, and were autopsied.

Blood changes: After primary implantations no regular blood observations were made, but after the second implantation, an increase in neutrophils and

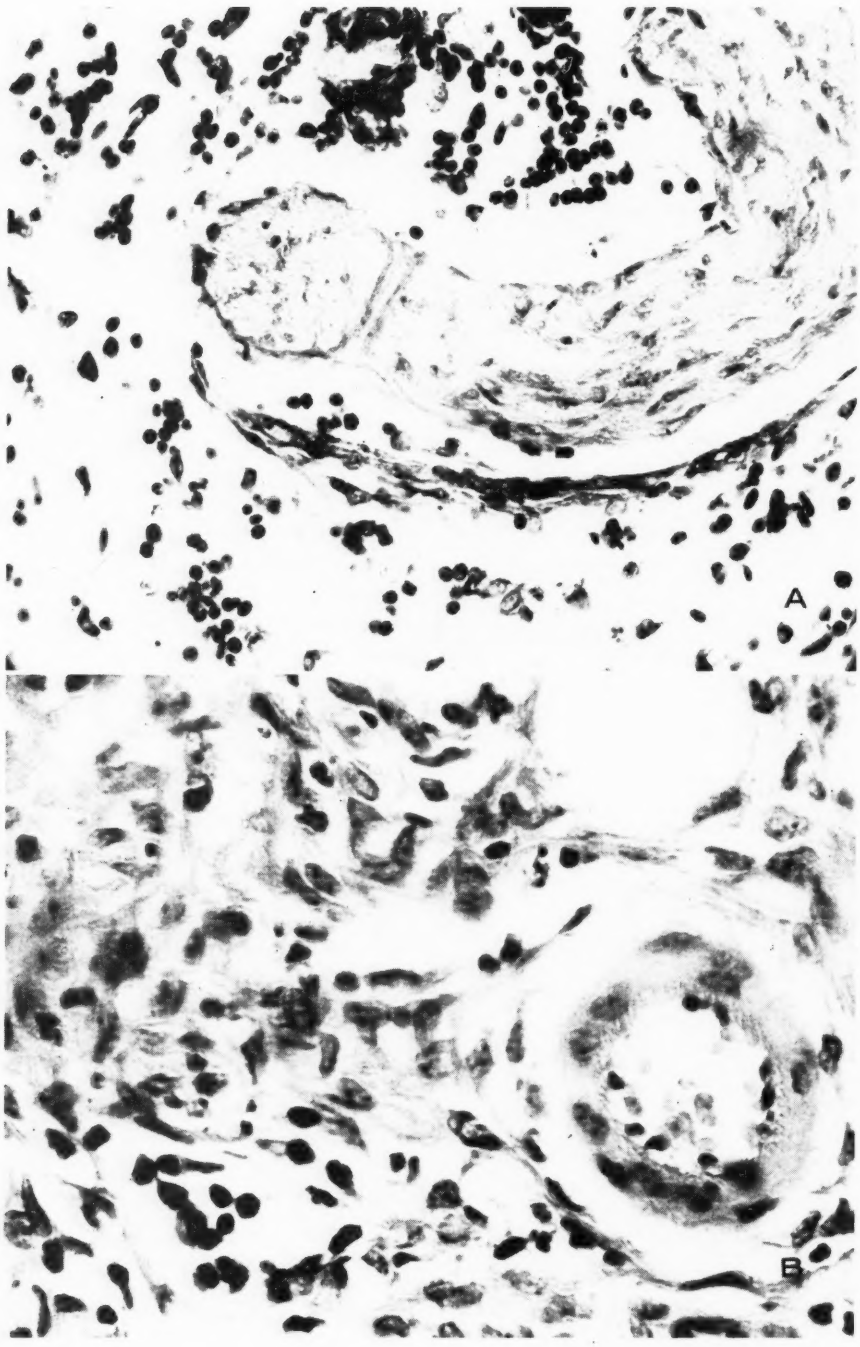

Fig. 3.—*A*, Accumulation of eosinophil leukocytes within dilated lymphatic channels in 48-hour lesion in unsensitized guinea pig (Exper. 2). There is now little or no emigration of leukocytes from the adjacent blood vessel. (Hematoxylin and eosin, × 980; reduced 3/7.)

B, Accumulation of eosinophil leukocytes in dilated perineural lymphatics in a 48-hour lesion in sensitized guinea pig (Exper. 3). (Giemsa, × 540; reduced 3/4.)

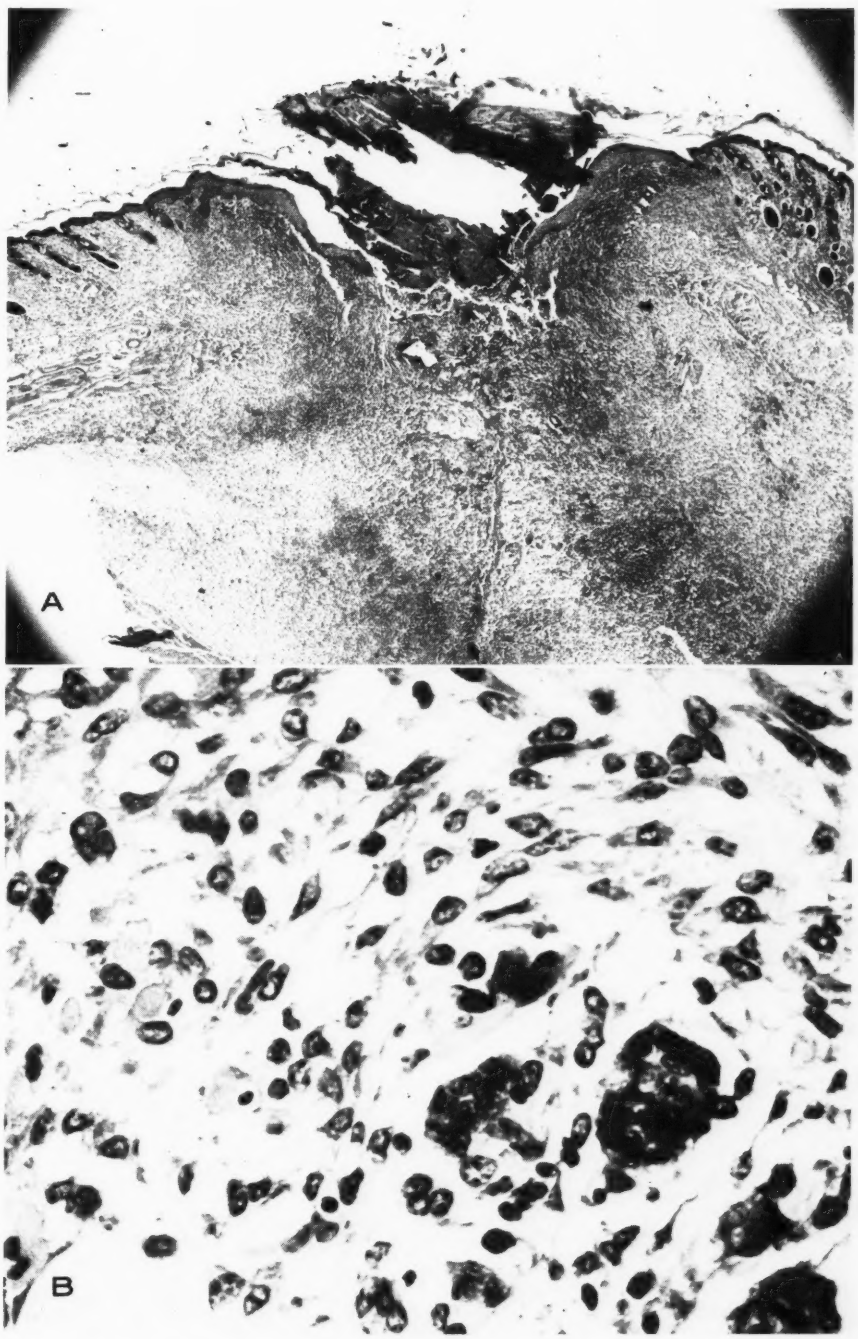

Fig. 4.—*A*, Fully developed granulomatous lesion at 6 days in sensitized guinea pig. (Exper. 3). (Hematoxylin and eosin, × 25; reduced ⅜.)
B, Detail of Fig. 4 showing giant cells. (Hematoxylin and eosin, × 980; reduced ⅜.)

fall in lymphocytes were observed in all but 3 animals. Eosinophils rose above initial levels in 16 animals, reaching abnormal levels in 7, normal levels being regained at 24 to 48 hours. Monocytes behaved irregularly, some transient rises being recorded; basophils showed no changes.

Exudates: In this experiment the course of cytologic events was almost identical to that of Experiment 2. A well-marked nuclear shift in neutrophils and some prominence of eosinophils were noted at 6 hours; monocytes, large and small lymphocytes, basophilic lymphocytes, and histiocytes were observed as before; no basophils were seen.

Skin lesions: Histologically, the lesion developed as in Experiment 2 with only minor differences. The histiocytic response was perhaps more rapid and a zone of epithelioid cells with occasional giant cells (Fig. 4, *A* and *B*) and peripheral fibrosis developed. Eosinophils were again scattered widely throughout the lesion and were observed within lymphatics (Fig. 3, *B*). No mast cells were seen.

DISCUSSION

Following implantation of Ascaris materials, the blood of most animals showed a rapid, transient neutrophilia and simultaneous fall in lymphocytes, initial levels being regained by 24 hours. Absent from control animals, these changes may be regarded as a response to the irritant substances, perhaps in the nature of a stress phenomenon as described by Whitby and Britton.[14] Eosinophils responded readily to polysaccharide but less promptly to protein implants. Though more potent in producing blood eosinophilia, the polysaccharide was less effective in producing tissue changes, this perhaps being related to its greater solubility. This solubility probably also accounts for the rapid disappearance of the material from the implantation site, either by absorption or exudation, and explains the poor cellular reaction in the tissues as the polysaccharide could be removed with minimal extravascular leukocytic activity. Under these circumstances, healing would be rapid and uneventful. On the other hand, the sluggish, more uncertain blood eosinophilia after the protein implant may reflect the slower release of chemotactic or eosinotactic substance, this implanted material necessitating preliminary breakdown by readily available biochemically potent elements—leukocytes. Hence the marked tissue infiltration by neutrophils with eosinophils following behind as disintegration of the protein progressed. In the study of these early events one can attempt to reconstruct the sequence of cell movements, and, in the light of accrued experimental knowledge, discuss cellular functions and the purpose of this reaction.

The Neutrophil Leukocyte.—After protein implantation, neutrophils, readily available from the body reserves,[15] increase in the blood stream, and, in the area of injury, sequestrate and become marginated in the dilated capillaries, as happens where endothelial cells are damaged,[16, 17] and thence pass into the tissues. In sections of the reaction at 3 hours, extravascular neutrophils, usually

mature segmented forms, lie along tissue planes in the direction of the implant; in more severe or prolonged reactions deeper tissue planes and vessels are also involved. The cells eventually reach the protein which is invested and subjected to enzymatic and phagocytic attack, the edges of the implant soon becoming scalloped and "moth-eaten." At 6 hours or later, early degenerative and necrotic changes appear in the neutrophils, and phagocytosis of nuclear remnants and granules by monocytes and histiocytes becomes increasingly evident. With the stimulus of these necroses the neutrophilic infiltration intensifies and less mature forms, including bands, metamyelocytes, and myelocytes, stream from the dilated vessels around the lesion. The implant is more deeply invaded and ova penetrated and disrupted while, with dark granules and vacuolated cytoplasm, neutrophils continue to degenerate and die. As the reaction subsides, about 36 hours or later, neutrophil emigration from blood vessels diminishes and ceases, these cells now being largely confined to the central inflammatory zone; histiocytic phagocytosis is very active there. Few neutrophils are seen outwith this area and are only infrequently encountered in outer tissue spaces or lymph channels.

The Eosinophil Leukocyte.—Slower to respond than neutrophils, eosinophils increase in the blood stream and pass into the tissues in the area of injury, moving toward the protein. Initially few in numbers, eosinophils slowly accumulate and are prominent in the later stages, when they are scattered throughout the area though more abundant in the outer part of the central zone. As emigration subsides they are, unlike the neutrophil, still seen in outlying areas, frequently within dilated tissue spaces or lymphatics. Sometimes eosinophils and histiocytes lie side by side and, occasionally, such a histiocyte, like others not associated with eosinophils, may contain irregular red cytoplasmic inclusions. Frequently observed,[18] particularly in hyperergic inflammatory states, this has been taken as evidence of histiocytic phagocytosis of the eosinophil.[19] The infrequency and variability of these findings and the morphologic characteristics tend to cast doubt upon this, although electron microscope studies, such as Welsh and Geer[20] used for mast cell granules, might be more definite. However interpreted, these were uncommon findings and the progression of eosinophils into the subcutaneous lymphatics would seem the normal sequel, perhaps with eventual re-entry into the blood stream.

The Monocyte.—No regular response of monocytes was observed in the blood stream but in sections, these were perhaps the earliest cells to emigrate from the vessels and to appear in smears of the wound exudate. These early arrivals soon engaged in phagocytic activity, acquiring cytoplasmic inclusions but, as the neutrophil infiltration increased, became less evident and apparently played little part in subsequent events.

The Histiocyte.—This designation is applied to a cell with round or slightly oval nucleus with diffuse fine chromatin and prominent nucleolus. The cytoplasm is abundant with an irregular outline and frequent protrusions,

sometimes long and filamentous like a fibroblast. Of a pale eosinophilic color, the cytoplasm frequently contained cytoplasmic inclusions—coarse and fine, acidophilic and basophilic.

These appeared late in the reaction, most commonly in the area underlying the zone of protein and neutrophils. No emigration of these cells from blood vessels was ever seen; instead they were formed locally by the proliferation of capillaries, these structures being known to retain much of their primitive multipotency, including phagocytosis and the formation of reticuloendothelial cells.[17, 18, 21] First accumulating in a loose arrangement, the histiocytes later formed a compact zone of cells around the disintegrating protein, some of the more centrally placed cells being phagocytic and occasionally formed giant cells. The deposition of a few strands of fibrous tissue around the periphery of the histiocyte layer completed the formation of the foreign body granuloma.

In unsensitized animals, tissue reactions similar to these have previously been produced by extracts of Ascaris and by live intact ova,[4, 22] but these did not appear for 14 days or more, this delay being held as evidence of an immunologic mechanism. In other Ascaris hypersensitivity studies, Speirs and Dreisbach[23] regarded some early eosinophilic responses as nonspecific. In contrast, the lesions studied here developed rapidly and the close similarity of the changes observed in both sensitized and unsensitized animals would seem to discount any significant immunologic influence. This property of being able to bring about changes firmly associated with immunologic mechanisms, such as anaphylactoid shock, eosinophilia, and granulomatous lesions, appears to reside in most derivatives of Ascaris tissue, including polysaccharide, polypeptides, and glucolipids[6] and, as we have seen, insoluble protein. Thus, it seems likely that in some or all of these materials lie the primary toxic factor or factors which initiate the pathologic events following antigen-antibody interaction. There are present in these lesions, changes associated with increased histamine, such as capillary proliferation and phagocytosis[17]; there are basophilic lymphocytes, which Tompkins[24] regards as evidence of sublethal nuclear damage, and the degeneration and necrosis of great numbers of neutrophil leukocytes, all of which suggest the local accumulation of cytotoxic substances. Also present is the eosinophil, a robust cell which can phagocytose such toxic material as histamine-rich mast cell granules[20] and can transport anaphylactogenic material in experimental animals.[7] It is seen within this unfavorable environment where it penetrates almost to the center of the lesion, persists in the tissue with little evidence of degenerative change, and emerges, apparently undamaged, to enter the lymph channels draining the area. These observations lend strong support to the concept of eosinophil function as an agent, absorbing, neutralizing, removing, or otherwise dealing with toxic substances perhaps lethal to other cells.

SUMMARY

The reaction in the blood and subcutaneous tissues of the guinea pig to implanted Ascaris polysaccharide and Ascaris protein has been studied.

Soluble polysaccharide produced a brisk eosinophilia of the blood with minimal response in the tissues. The insoluble protein produced erratic minimal changes in the blood eosinophils but stimulated a well-marked tissue reaction of the foreign body granuloma type in which eosinophils were prominent.

The observed sequence of histologic events yields valuable clues to the parts played by the individual cell types and to the essential nature and purpose of the tissue reaction.

The true nature of eosinophil function and its pathologic significance are tentatively discussed.

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THE VALUE OF THE COCA PULSE-ACCELERATION METHOD IN FOOD ALLERGY

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IN 1942, Coca, in a book entitled *Familial Nonreaginic Food Allergy*,[1] reported the results of his studies[2] of allergic patients in whom intracutaneous skin tests are negative and skin sensitizing antibodies (reagins) are absent. According to Coca, these patients developed abnormal pulse-rate increases after the ingestion of a food to which the patient was allergic, whereas the rate remained within the patient's normal range if allergy to that food did not exist. Elimination of those foods causing abnormal pulse increases (pulse-acceleration) was followed by symptomatic relief in practically all of those cases in which food allergy played a major role.

Basic figures of the average adult pulse rate had been derived previously from such studies as those of Peterson and Walter[4] in which one or two observations were made on 1,200 subjects, and the standards given as 66 per minute for men and 74 per minute for women. Coca also carried out an extensive study of the pulse rate in which 14 to 22 counts were made daily on each subject over periods of weeks or months. The subjects were nonallergic individuals and/or food-allergic patients from whose diets and environment the incriminating allergens had been removed. From the results of these studies, Coca drew the following conclusions: (1) There are wide variations in the normal rate. Rates below 50 and a little above 80 can occur in healthy individuals, but are infrequent. (2) Statistically, there is a negligible difference in the rates of men or women. (3) The variation in the rate from low to high, or the range, was 12 beats per minute or less in most individuals. A few had a range of 14, and, very exceptionally, a range of 16. (4) The average minimal rate was around 62 per minute, the average maximal rate around 72 per minute. (5) In normal individuals (including those with food allergy but free of the influence of allergens), the pulse rate rarely exceeds 84 per minute. In the sense used, normalcy includes freedom from infection, fever, hyperthyroidism, stimulation by nicotine, drugs, physical activity, acute emotional disturbance, etc. Thus, to quote Coca: "For each individual there is a pulse-character defined by its general level, its range

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(lowest to highest rate) and the constancy of its daily maximum." Knowledge of these principles is necessary in order to establish a base line from which abnormal variations can be judged.

Coca's initial reports were not accepted by most allergists who privately expressed doubt and skepticism about the method. They questioned his findings as to the normal pulse range, and the lack of control over such influences as exercise, emotion, and complicating infections. Further criticism arose when half-hearted and incomplete attempts to use the method resulted unsuccessfully. In addition, general opinion regarding the method's value was not enhanced by Coca's claim that the method would help to detect nonreaginic food allergy factors in many conditions not previously regarded as allergic, such as hypertension, multiple sclerosis, glaucoma, and even certain types of cancer[5]; also by his claim that failure of a patient to respond to dietary elimination of pulse accelerators may be due to extraneous influences such as the inhalation of dust, or smoke, or the use of aluminum cooking utensils; and finally, by Coca's claims of the value of sympathectomy in intractable cases.

Despite general skepticism regarding the method, we continued to believe that it basically might be of value and worthy of trial, especially since no comprehensive studies have been reported since Coca's original publications in 1939 which disprove Coca's findings and contentions. His report of the detection of clinical food allergy tested by his method in patients with negative skin-test reactions to foods was in keeping with the recognized observation that patients often improve after removal of certain foods from their diets to which negative skin-test reactions are obtained. Many of us have been aware of the need of more objective methods of determining food allergy than those currently employed. Such determination depends greatly upon dietary changes and upon observations made primarily by the patient at home and interpreted secondarily by the allergist. A step in the direction of objective observation is the provocative testing procedure of Rinkel, Randolph, and Zeller.[6] In their method, the food to be tested is completely avoided for 4 days, and then fed on the fifth day. The patient then is watched closely for development of symptoms and of leukopenia. In the absence of clear-cut symptoms, these investigators place much value on the latter finding which they claim is significant under their conditions of testing. Earlier experiences with the old leukopenic index, based on the hemoclastic crisis of Widal, makes it extremely doubtful that the induction of leukopenia can be regarded as a reliable indicator of allergic reactions to foods.

Intracutaneous skin tests, if specific and positive, can help to determine food sensitivities; but the frequency with which nonclinical positive skin test reactions are obtained and the frequent occurrence of negative reactions in the presence of proved sensitivity limits the value of skin tests in the determination of food allergy. In the nonreaginic patient, skin tests are valueless.

It seemed to the authors that if the Coca method could be substantiated it might provide a welcome addition to our diagnostic procedures. Its possible advantages appeared to be that the method was objective, easy to carry out, and required no special equipment. Also, since single foods are fed at intervals of 1½ hours, any abnormal pulse readings which are obtained could be attributed to the effects of the last food ingested. This renders interpretation easier than in those methods where meals consisting of many foods are eaten. More than 2 years ago we began to use the pulse acceleration method as part of a complete study of certain patients in whom food allergy was suspected and intracutaneous testing with food allergens yielded completely negative or doubtful responses. The results of these investigations form the basis of the present report.

METHOD OF STUDY

In the cases reported by Coca and by others[7, 8, 9] it never is specifically stated whether the numerous pulse readings recorded in each case were obtained by the investigators or by the patient. Early in our study we realized that, with rare exceptions, our patients could not be relied upon to make accurate pulse counts. Thus we instructed a few patients in the method of taking their pulse and asked them to practice doing this at home. When they returned to the clinic for testing, we again had them count their own pulse rates in the clinic and checked those with the ones we took immediately afterward. The readings differed so significantly from our own in some of the patients (a total of 6) that we decided in the future to take all the pulse readings ourselves; hence, the figures recorded in this study have been obtained by one of us (L. N. E.). The pulse-dietary studies were carried out in a room in our out-patient allergy clinic where environmental conditions, such as inhalation of dust, tobacco smoke, etc., could be kept at a minimum, where the types and amounts of foods for testing could be rigidly controlled, and where the development of symptoms could be directly observed.

In all other respects we followed closely the directions given by Coca. Each patient was instructed to report to the clinic in the early morning. No food or liquid (except water) was allowed after the last meal of the preceding evening; also no medication and no smoking* was allowed for 24 hours prior to the tests. Testing was continued until late afternoon, which made it possible to test from 4 to 6 foods each day. Eight or more of these all-day sessions were required for each patient in order to test the foods commonly included in the diet.

Upon arrival, the patient is allowed to sit for 5 to 10 minutes before the initial feeding. Then a single food is given, and pulse readings are taken immediately before, and at intervals of ½, 1, and 1½ hours after the food ingestion. Another single food is then administered and readings similarly made. The procedure is continued with different foods until late afternoon.

*It is essential to forbid smoking before and during the testing period since prolonged pulse-rate increases from nicotine would result.

Whenever possible, foods are tested in pure form rather than mixed with other foods or with spices or flavoring agents.* For example, in testing wheat we prefer to use a pure wheat cracker or cereal rather than bread. Salt is permitted, when needed to improve palatability, as with egg or celery.

All pulse readings† were taken after the patient had been sitting for at least 3 minutes. Experience has shown that the pulse rate will return to its pre-activity level during this period. Between readings the patient was allowed to walk around as desired.

In those patients who showed little or no pulse variation after the first few foods were tested, the testing procedure could be shortened somewhat by taking two post-ingestive readings at ½ and 1 hour intervals instead of the usual three, thus testing a new food at hourly intervals. It always is necessary to wait for the pulse to return to the normal range after a positive response before testing another food. After a positive pulse acceleration, the reaction usually wears off within 1½ hours after ingestion, and the testing procedure may be continued.

We used no prescribed order in testing the different foods. As recommended by Coca, we avoided at first those foods which might disagree with the patient. Milk was one of the first foods tested since, if it proved to be nonallergic,‡ it would be a good sustaining food in a patient with multiple food sensitivities. Thereafter, wheat, orange, egg (hard boiled), potato, beef, corn, and other common items in the diet were tested. The food to be tested was given in accordance with Coca's instructions in an amount approximately one half to three quarters of a normal serving; for example, 1 egg, ½ glass milk, etc. For easier administration, a negative reacting food sometimes was given together with an untested food; such as tomato juice containing pepper (untested), milk with dry cereal (untested), etc.

As we gained experience in doing the tests, we encountered some difficulties not mentioned by Coca or others using the method. Thus, for example, while restriction of activity to sitting or walking, interdiction of smoking 24 hours before and during the test period, and the absence of home inhalant factors in the clinic testing room all serve to bring the pulse rate within the patient's normal range, we found asthmatics who are allergic to numerous inhalants and who use pulse excitatory drugs particularly difficult to study. Such patients may require 1 or 2 hours of rest in the clinic before starting the test procedure. In the meantime, it was found advantageous to feed them small amounts of single foods of low sensitizing capacity or previously tested negative foods merely to allay hunger while waiting for the pulse to return to a rate within normal range.

It was not feasible for us, except in a few hospitalized patients and in the cases of a few exceptionally qualified patients, to obtain accurate pulse

*Food items in proper form for this study were supplied from the hospital diet kitchen through cooperation of Mrs. S. M. Smith, Secretary of Dietary Service.

†In order to take the radial pulse with the required degree of accuracy, 30 or 60 second counts were made, using a watch with a large sweep hand. Abnormal counts were repeated and the recorded figure is the average of 2 or 3 successive readings.

‡In the pulse acceleration method, this means, of course, the absence of an abnormal pulse increase following food ingestion.

rate readings immediately upon awakening and before getting out of bed. This figure is of paramount importance in determining the lowermost rate of the pulse range. We were able to determine from readings on the above-mentioned patients that the latter figure averaged 4 beats less than the lowest figure obtained during the course of 3 successive testing days. We, therefore, subtracted 4 from the lowest figure and took this to represent the rate upon awakening. Thus, if the lowest pulse rate obtained in three sessions of testing was 68, the daily minimal rate was assumed to be 64. By adding 12 to this figure, the patient's (normal) basic range would be estimated to be 64 to 76. Twelve is added because from previous determinations by Coca, confirmed by us, it is the average range of the pulse rate in the normal non-allergic individual.

ABERRANT REACTIONS

Coca describes several aberrant pulse responses; and, in this respect, the pulse-dietary method would appear to be heir to all the atypical and sometimes confusing results obtained by other methods of determining food sensitivity. Thus, there may be lack of pulse increase after ingestion of a known allergenic food because of refractory periods, and exhaustion of the shock organ (in this instance, the pulse-accelerating mechanism); there may be pulse increases after the ingestion of a nonallergenic food because of a recurrent reaction from a food consumed several hours previously; there may be positive responses to foods which previously gave a negative response, this being due, according to Coca, to the manifestation of minor food allergies after removal of major offenders from the diet; and so on. If these so-called aberrant reactions occurred frequently, one would have to resort to guesswork in interpreting the results; in fact, one would be justified in questioning the validity of the principle of allergic tachycardia. In our work, these atypical types of pulse responses were uncommon.

If the patient had pulse irregularities, as happened occasionally, the average of three successive counts was recorded. In patients with skipped beats, experience showed that inclusion of the skipped beat in the counting yields a more accurate figure.

It should be remembered that in this method of testing, pulse acceleration above the normal range is the sole index of hypersensitivity to the ingested food. It is completely independent of the induction of symptoms, which in our experience seldom follows immediately after the ingestion of the tested foods. (Exceptions will be seen later in Cases 1 and 4.) However, induction of symptoms may appear later after the testing session is over and after the pulse has returned to normal. It should be emphasized, however, that the induction of symptoms is not an important part of the testing procedure, which depends solely on pulse acceleration. This is similar to a patient having a positive skin test reaction to a food allergen without the test inducing any systemic symptoms. In the occasional instances in which

symptoms followed the ingestion of a pulse-accelerating food, additional evidence of hypersensitivity thus was obtained.

RESULTS

Fifty-two patients were studied over a 2-year period in our clinic under conditions in which, as already indicated, all the testing was under our personal direction, and all pulse counting was done by one of us (L. N. E.). These patients were predominantly food nonreaginic; that is, they had negative intracutaneous tests with food allergens. All patients presented symptom pictures that either were truly allergic (such as, asthma or urticaria) or sometimes are attributed to allergy (for example, headaches).

Of the 52 patients, 19 had what we considered to be complete studies—that is, they had food trials with all the major foods in their diets, and, in most of them, the positive reactors were rechecked at least once.

The remaining 33 patients had only partial studies, and therefore are not included here in the final results. However, the latter group did contribute to the over-all evaluation of the method. In some of these patients, improvement followed removal of some of the pulse-accelerating foods from their diets.

Among the 19 completely studied patients, chronic asthma was the major allergic problem in 13, chronic urticaria in 3, migraine in 2, and chronic rhinitis in one. Improvement as the result of elimination of pulse accelerating foods was noted in 6 of the asthmatics, one patient with migraine, and one patient with urticaria; no improvement was noted in 4 asthmatics, one patient with urticaria, one with migraine, and one with allergic rhinitis. Four patients (3 with asthma and one with urticaria) showed no pulse accelerating foods, and presumably had no food allergic factors.

CASE REPORTS

The following case reports have been selected to illustrate both the method of study and the end-results obtained in some of the patients of the group of 19 completely studied.

CASE 1.—T. B., male, 58 years of age, had severe asthma of 10 years' duration complicated by moderate emphysema. Desensitizing procedures had been given, but without benefit. Because of negative skin tests to foods, a negative clinical history of food allergy, and unsuccessful attempts at diet trial, it was concluded that foods played no part in the production of his asthma. At his first session with the PA* method, it was found that milk increased his pulse to 92, a figure which later study showed to be well above his normal range (66 to 78). At his second session, beef and pea were found to elevate his pulse above the normal range. He then recalled that on two occasions acute asthma occurred after a dinner consisting of ham, cabbage, and potato. At the third session, ingestion of ham gave a negative response, but after eating cabbage he had an abnormal pulse rise at the ½ hr. reading, and at the end of ¾ hour the PR† was 94—in addition he developed an acute attack of asthma. At the next testing session, potato also gave

*PA = pulse acceleration.
†PR = pulse rate.

a positive PA, but no asthma followed. We assumed, therefore, that the acute asthma which followed the dinner of ham, cabbage, and potato probably was provoked by the simultaneous ingestion of two potent allergens, cabbage and potato. After further testing, a few more PA foods were detected and all of these are now eliminated from his diet (milk and its products, beef, pea, peanut, cabbage family, salmon, potato, oyster). In the 10-month period since the patient began eliminating the PA foods he has definitely improved. Whereas he formerly had asthma daily, he now has only minimal asthma symptoms, acute attacks being provoked by exposure to inhalants (mold, ragweed, etc.), or by indiscretions in his diet. We had a good opportunity to witness directly this patient's extreme sensitivity to one of the inhalants. On one occasion, while he was sitting in a cubicle undergoing the ingestion tests, a technician carrying a funnel containing a large mass of powdered house dust accidentally passed close by him. Within a few minutes the patient began having a severe asthmatic attack, requiring epinephrine by injection to relieve him. This incident, of course, precluded the continuation of further testing for that day. When this patient's asthma is in a quiescent state, it has been noted that his PR averages around 72 per minute, whereas, when he is in a period of exacerbation, his PR is about 90.

This case report is a good example of an instance in which the detection of food allergy was accomplished solely by the PA method since previous attempts at diet trial failed to determine these same food factors. Elimination of the PA foods from the diet resulted in definite improvement in a patient in whom inhalant allergens also played an important etiologic role. This case also illustrates the difficulties encountered at times in performing the PA tests in a patient whose asthma from other causes produces increases in the pulse rate beyond the normal range.

CASE 2.—J. K., male, 58 years of age, had asthma of long duration, as Case 1, with positive reactions to inhalant allergens for which he had been receiving the indicated hyposensitizing procedures. He had negative skin tests to foods, and showed little improvement even after long-continued treatment. He was studied by the Coca method with some difficulty, and we were unable to elicit any characteristic pulse-acceleration after feeding of the common allergenic foods. On several occasions the patient reported to the clinic in an asthmatic state, with a high pulse rate, making it useless to proceed. However, over a period of 6 months, there were enough occasions when the pulse rate was considered near or within the normal range to conduct the tests, and sufficient testing was completed to determine that foods apparently played no role. This man's asthma has continued unabated, despite hyposensitization treatment.

CASE 3.—L. D., a 50-year-old woman, had had perennial allergic rhinitis, seasonal hay fever, and occasional asthma since 1930. Positive skin test reactions were obtained to dust, timothy, and plantain, with negative reactions to all foods. For many years she had definitely associated her perennial rhinitis symptoms with the ingestion of certain foods (onion, apple, canteloupe, peach, watermelon, rice, milk, ice cream). The latter foods were tested by the PA method and all of them were found negative. But tomato and peanut which the patient had not suspected as causing clinical symptoms were found to be positive pulse accelerators. To eliminate the possibility that long abstinence might have lowered the patient's sensitivity, we had the patient consume some of the first-named items several times during the week preceding the retesting procedures. There was neither exacerbation of symptoms at home, nor positive PA after retesting in the clinic. However, symptoms in this patient definitely were provoked repeatedly after eating tomato or peanut. Yet these were foods that were never suspected as being causative by the patient and were negative by intracutaneous skin test.

Although this case illustrates the unreliability of the clinical history in some patients and the demonstration of unsuspected food allergens by the PA method, the patient was not materially benefited by the elimination from her diet of all tomato products and peanut.

CASE 4.—C. E., a 32-year-old woman, had frequent migraine headaches (associated with nausea, weakness, and pallor), and more or less continuous nasal blockage, considered to be allergic in origin. During one of the testing sessions, the feeding of salmon was followed by a pulse increase to 94, well above the normal range (64 to 76). Concomitantly, she developed headache, pallor, and weakness, typical of her migrainous attacks. Of a total of 40 foods eventually tested in this patient, 27 of them (amounting to 67 per cent) induced PA above the normal range. To remove all of the PA foods from her diet would have resulted in severe dietary restriction totally unpleasant to the patient and practically impossible to pursue faithfully. Under the circumstances the patient was advised to eliminate only those PA foods which she knew to cause symptoms, such as salmon, egg, and a few others. On this regime, plus occasional doses of Phenergen, she noted improvement.

This case report illustrates one of the difficulties encountered at times in patients who seem to have sensitivity to so many foods (whether detected by skin testing or by the PA method) that complete elimination becomes impractical or impossible. Elimination of the more important ones without impairing the nutrition of the patient, supplemented by symptomatic treatment, is the only practical solution to this problem. The reason for the occurrence of such multiple sensitivities is not clear.

CASE 5.—W. W., a 55-year-old woman, had frequent headaches and nasal symptoms attributed to a perennial allergic rhinitis. In contrast to Case 4, test feeding of all the common food allergens provoked hardly any change in her pulse rate. It continued at the rate of 58 to 60 throughout all testing sessions. We concluded therefore that food allergy probably was unimportant etiologically in this patient.

COMMENT

Although only 19 out of 52 patients had complete pulse studies, some of those considered as incompletely studied finished 50 per cent or more of their planned tests, and thus may be included in the over-all evaluation of the method. On the basis of our total experience to date, cases seem to fall into the following categories:

I. Those in which most of the foods tested are pulse accelerators (exemplified by Case 4). This was true in 4 patients of the total of 52 studies.

II. Those in which no PA foods can be found (exemplified by Case 5). This was true in 8 patients.

III. Those in which a few or moderate number of PA foods are found and their removal results in (a) improvement (exemplified by Case 1) or (b) no benefit (exemplified by Case 3). Since many patients in Group III failed to complete the pulse studies, it was not possible to classify these patients accurately. Of the 19 patients completely studied, 8 patients improved after removal of pulse-accelerating foods, 6 failed to benefit, and 5 had negative tests.

The patients in Group I, in whom most foods produced pulse acceleration, were the ones in whom Coca advised lumbar sympathectomy as a remedy. We definitely do not subscribe to any such view. Patients in Group II probably did not have food allergy, although in the absence of a better method of determination this would be mere supposition.

The patients in Group III (a) are the most important of all the patients studied since the results obtained in this group would seem to bear out the validity of the pulse-acceleration method of determination of food allergy. In these patients it was possible to determine that they apparently were allergic to foods to which they had negative skin test reactions; but removal of these foods from the diet was followed by relief of symptoms, whereas the latter were provoked by their re-addition. Such foods produced definite pulse acceleration beyond the normal range not only when first tested but even after repeated tests. Our results, at least with this small group, would seem to verify Coca's claims that under proper conditions of testing, the single addition of certain foods to the diet will induce definite increase in the pulse rate beyond the normal range. It might be argued that this does not necessarily prove that the pulse rate increase is a sign of allergy but that it could result from some other mechanism. No one could dispute such an assertion, except that when pulse-accelerating foods subsequently were added back to the diet they provoked symptoms. When this happens during the course of other methods of diet trial, the patient is considered to be allergic to such symptom-provoking foods. It would seem similarly justified upon the basis of the results of the pulse tests to assume that the abnormal pulse-acceleration induced by certain foods could be the result of an allergic reaction; also that the pulse acceleration method is a valid means of detecting food allergy.

By contrast with the patients in Group III (a), those comprising Group III (b) also had positive tests with certain foods. But when the pulse accelerating foods were removed from the diet, no improvement was noted. Whether this was due to such extraneous influences as exposure to inhalant allergens, as Coca believes, or to other unexplained causes, is problematical. This experience is not unusual in other methods of diet trial used for diagnostic purposes and does not invalidate the fact that ingestion of certain foods can accelerate a patient's pulse rate.

The amplitude of the pulse increases in a positive response, referred to by Coca as "allergic tachycardia," is not great, as can be noted in Figs. 1, *A* and *B*. In the 52 cases in this series, we did not find the pulse speed-up to the degree reported by Coca. This discrepancy possibly can be attributed in part at least to the fact that Coca's patients counted their own pulse rates whereas we counted them ourselves.

The nature of the mechanism involved is still conjectural and has not been clarified by experimental studies. The pulse acceleration begins rather quickly, often within ½ hour after ingestion; and Coca reports instances in which it was detectable within 5 minutes. The typical reaction of pulse

acceleration and subsidence to the normal range occurs within a period of 1½ hours, usually without participation of the sensitized cells of the affected shock organ. But occasionally, as exemplified in our case reports, symptoms such as asthma will occur simultaneously. There does not appear to be any relationship to metabolic stimulation by protein food, since negative PA may follow the ingestion of such foods as meat, eggs, fish, etc.

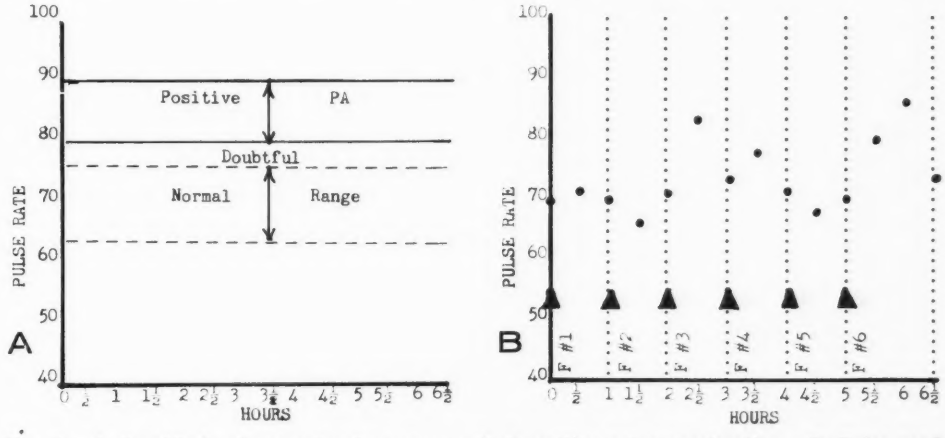

Fig. 1.—*A*, Amplitude of normal pulse range and of positive pulse acceleration. *B*, Pulse readings in a typical testing session, hourly feedings (F = food).

Our experience with this method revealed certain serious drawbacks to its use in the diagnosis of food allergy in clinical practice. It is time-consuming, requiring from 6 to 8 or more all day sessions for its completion. Furthermore, as already indicated, the test must be carried out under ideal conditions which include the absence of irritant environmental factors (such as, exposure to dust, tobacco smoke, etc.); in addition, the patient must not take any medication prior to the testing, and the tests cannot be done on days when the patient is having active symptoms, thus prolonging the test period. These hindrances prevented the completion of our studies in 33 of the 52 patients in our series, especially since most of them were clinic patients and reported only once a week for testing. Coca probably was able to finish the tests more quickly because the patient did the pulse counting, whereas, for reasons already stated, we took the readings ourselves in all but an occasional patient. If the readings could be taken by a trained person (such as a nurse or technician) and the patient be tested daily under controlled conditions, as for example in a hospitalized patient, application of the method might be rendered less difficult. Despite these drawbacks, our studies indicate that this method of diagnosis might have a place in the determination and study of food allergy.

SUMMARY

Fifty-two allergic patients were subjected to the Coca pulse acceleration method for determining specific food sensitivities. The entire testing pro-

cedure was carried out under what we considered ideal conditions, and, to insure accuracy, all pulse readings were taken by one of the investigators. Complete testing of all commonly eaten foods was done in 19 out of 52 patients and the effects of removing pulse accelerators from their diet evaluated. Of 13 asthmatics who completed the studies, 6 improved by removal of pulse-accelerating foods, 4 failed to benefit, and 3 showed no evidence of abnormal pulse increase after food ingestion. In 3 patients with chronic urticaria, one improved after elimination of the pulse-accelerating foods, one was unimproved, and the third patient had no pulse-accelerating foods. One of 2 patients with migraine was benefited and one patient with chronic allergic rhinitis failed to improve. The results of our studies would seem to verify the validity of Coca's claim that, in certain patients, foods can act as pulse-accelerators and that such an effect probably is on an allergic basis. Clinical application of the method is beset with certain drawbacks which greatly limit its usefulness in clinical practice. Its value as a method of diagnosis in food allergy will have to be determined by further investigation and clinical application.

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ALLERGY

C. von Pirquet

In recent years there has been collected a series of findings concerning hypersensitivity in the immune organism, which belongs to the field of immunity, but which this term describes badly.[1]

These expressions conflict with one another: while an immune organism is understood to be protected against a disease, to be affected by it no more; at the same time shall this organism be considered hypersensitive to the same disease?

Von Behring had already been aware of this contradiction, when he designated as the "paradoxical reaction," the death of an animal with great immunity against tetanus, from a small quantity of the same toxin.

We may, however, consider this "paradox" only as an exception; the farther one penetrates into this field, the farther the general law extends, and we recognize a great number of disease processes at present, in which symptoms of hypersensitivity are met with.

Herein belong tetanus (v. Behring, Kretz), tuberculosis (Courmont, Strauss and Gamaleia, Babes and Proca, Detre-Deutsch, B. Schick, Löwenstein and Rappaport, Müller, Löwenstein and Ostrowsky), syphilis (Finger and Landsteiner), diphtheria (Rigt), serum (Arthus, v. Pirquet and Schick, Lehndorff, B. Otto, Rosenau and Anderson), bacteria in general, organ extracts, various proteins and hay fever (A. Wolff-Eisner).

But are immunity and hypersensitivity really connected with one another? Are the processes by which pretreatment produces immunity to be separated from those which lead to hypersensitivity?

A. Wolff-Eisner[2] desires to maintain this separation: the processes, in which toxins are implicated, lead to antitoxin formation and immunity, those processes, in which endotoxin represents the active agent, lead to hypersensitivity.

But we already see from experience with tetanus that hypersensitivity can occur with pure antitoxic processes. Wolff-Eisner's objection that it occurs only as an exception appears to me to miss the principle of the question.

Richet,[3] who was the first to recognize the importance of hypersensitivity, which he called anaphylaxis, found, that injection of his actinia poison begot immunity and anaphylaxis equally: with the re-injection of the toxin after a

An historical document first published July 24, 1906, in Muenchener Medizinische Wochenschrift, volume 53, No. 30, pp. 1457-1458. Permission to translate granted by J. F. Lehmanns Verlag.

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certain time, the animal usually dies suddenly; but if they survive the first shock, they get over the disease more rapidly than control animals injected once.

Von Pirquet and Schick[4] have drawn similar conclusions from serum sickness: the phenomena run their course in a more stormy, but in a more rapid, manner after re-injection.

Recently, Rosenau and Anderson[5] have pointed out that, in spite of enormous hypersensitivity which guinea pigs acquire through injection of minutest amounts of horse serum, immunizing processes accompany this hypersensitivity; if, instead of injecting only once, one repeats the injections of horse serum through 10 days, then the animals injected ten times do not succumb from the later re-injection of horse serum, as do those pre-injected only once.

The connection between immunity and hypersensitivity appears to me to be elucidated most clearly from experiences with vaccination.[6] The person vaccinated a short time before appears hypersensitive as opposed to the one being vaccinated for the first time, for he reacts much more quickly to the infection, yet simultaneously he is protected, for in his case the vaccinal process only develops a slight local extension, and he is spared all general manifestations. Finger and Landsteiner[7] have discovered just recently quite similar relationships in the case of syphilis. Re-inoculation with syphilis has a distinct effect in all stages. This appears more swiftly than after a first infection (shortened incubation period); with tertiary syphilis a local erythema can even appear at once after the re-inoculation, an event which may be equated with the "immediate reaction" of repeated serum injections.

Consequently, immunity and hypersensitivity can be most intimately bound together.

These words are in contradiction to one another, for their union is entirely compulsory. Yet the immunity conception was taken over from the time when one still did not know hypersensitivity.

But now the fact is (as F. Hamburger[8] says) that the specific change, which an animal suffers after an experimental sickness, increases sensitivity almost as often as it increases resistance.

We need a new, general, non-prejudicing word for this altered state which the organism experiences through exposure to some organic, living, or lifeless poison.

The vaccinated person behaves with regard to the vaccine, the luetic with regard to the syphilis virus, the tuberculous patient with regard to the tuberculin, the one injected with serum with regard to the serum in a different manner than does an individual who has not yet come in contact with the agent in question; they, however, are still far from nonsensitive. All that we can say about them, is that their ability to react is altered.

For this general concept of altered reactivity, I propose the term "allergy." Allos denotes the deviation from the original state, from the behavior of the normal, as in allorhythm, allotropy.

The vaccinated one, the tuberculous one, the one injected with serum becomes allergic to the respective foreign substance. Again, a foreign substance

which influences the organism to cause a variation of the reaction, through one or repeated exposures, is an allergen. In an unphilologic way, to be sure, the term has to lean upon the term "antigen" (Detre-Deutsch), which means a substance which may cause the production of antibodies. The allergen concept reaches farther: besides the antigens, numerous protein substances are allergens, though they cause no antibody formation they do lead to hypersensitivity. Allergens are all exciters of infectious diseases, which are followed by immunity: also the poisons of the gnat and bee shall be reckoned with as allergens, in so far as under- or over-sensitivity occurs after a sting. On this basis, the pollen of hay fever (Wolff-Eisner), the urticaria-producing substances of strawberries and crayfish, and probably also a series of organic substances which lead to idiosyncracy, could be united under this name.

The designation "immunity" shall be limited to those processes where the introduction of the foreign substance into the organism gives no clinical reaction at all, where, therefore, a perfect insensitivity is present, whether this be conditioned by means of alexins (natural immunity), by means of antitoxins (active and passive immunity against diphtheria and tetanus), or by means of a kind of adaptation to the poison (Wasserman and Citron).

The new name does not encroach upon the previously existing special nomenclature. The delimited notion of the antitoxins, cytolysins, haemolysins, precipitins, agglutinins, coagulins is not touched. Hypersensitivity is a new area of work in which only in recent years has the formation of these concepts taken place under wearisome adaptation to the old names. Because of the need to bring clarity to this concept, I propose this new designation and hope that I shall create new collaborators by the simplification of the external forms and an easing of the study of the interesting processes in this field.

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SWEAT ELECTROLYTES IN ALLERGIC CHILDREN

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SWEAT electrolyte determinations were found to be useful in the diagnosis of cystic fibrosis of the pancrease by Darling and co-workers[1] in 1953. Their results were confirmed by other investigators. Within the last few years, there has arisen some interest in the possible association of allergy with cystic fibrosis of the pancreas and, accordingly, attempts have been made to determine if sweat electrolyte levels are elevated in the allergic patient. Conflicting reports have appeared on this point. The purpose of this report is to present our data on the concentration of electrolyte (chloride) in the sweat of allergic children.

PATIENT MATERIAL

Fifty-five patients with allergic conditions were tested. Among this group were 41 asthmatics, 12 patients with allergic skin conditions, and 2 with allergic rhinitis.

A control group consisted of 70 patients who were believed to be free from any condition that would cause an elevation of sweat electrolytes. The majority were apparently normal children and the remaining ones had been hospitalized for treatment of fractures, circumcisions, tonsillectomies, and hernioplasties.

PROCEDURE

The procedure of Gibson and Cooke,[2] utilizing pilocarpine by iontophoresis, was used for performing the tests. The sweat was collected on 3 by 3 inch squares of cotton gauze. Four milliliters of a 0.10 per cent pilocarpine nitrate solution was iontophoresed with a current of 4 Ma. for 15 minutes. The collection periods varied from 30 to 60 minutes.

The tests for chloride on the samples were performed according to the method of Schales and Schales.[3] The principle involved titrating the sample with standard mercuric nitrate solution at the proper acidity in the presence of diphenylcarbasone as indicator. Chloride present reacted with the added mercuric ions to form soluble but undissociated mercuric chloride. An excess of mercuric ions gave an end-point of a purple hue.

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RESULTS

The results are summarized in Table I. The upper limit of normal for chloride in sweat was set at 80 mEq. per liter for this study.

TABLE I. RESULTS OF SWEAT TESTS IN ALLERGIC PATIENTS AND CONTROLS

	SUBJECTS (NUMBER)	MEAN SWEAT CHLORIDE (MEQ./L.)	MEDIAN SWEAT CHLORIDE (MEQ./L.)
Controls	70	35.26	34
Allergic patients	55	46.07	35

For further analysis of the data the subjects were divided into three age groups as shown in Table II. There was a slight trend toward increase in sweat chloride with advancing age among the allergic patients. This, however, was not true with the controls.

TABLE II. COMPARISON OF SWEAT CHLORIDE IN ALLERGIC PATIENTS AND CONTROLS BY AGE

CATEGORY	NO.	AGE (YR.)	MEAN SWEAT CHLORIDE (MEQ./L.)
Allergic patients			
I	16	under 6	43.0
II	18	6-12	46.5
III	21	over 12	48.0
Controls			
I	32	under 6	39.8
II	25	6-12	35.0
III	13	over 12	24.2

Another interesting observation was the fact that in both categories of patients, that is, allergic and controls, the females tended to have higher values in at least two out of three age divisions.

DISCUSSION

In 1958, Hsia and co-workers[4] reported finding an increase in sodium and chloride in the sweat of patients with allergies. Using the conventional sweat test, they found that sweat sodium was 45.4 ± 4.2 mEq. per liter among 32 allergic patients, as compared with a value of 21.7 ± 1.9 mEq. per liter for 83 normal controls. Likewise, the sweat chloride was 38.6 ± 3.3 mEq. per liter in 31 allergic patients, as compared with a value of 19.5 ± 1.3 mEq. per liter for 83 normal controls. These investigators stated that the sweat electrolyte abnormalities were unrelated to age, sex, race, type of allergy, or medication used by the patient.

Subsequent investigators[5, 6] have not been able to confirm the significant difference in sweat electrolytes between allergic and normal individuals, as reported by Hsia and his colleagues. In Table III, the results of 4 different studies are listed.

Although no acceptable physiologic explanation for the pathologic elevation of electrolytes in sweat has been given up to the present time, nevertheless, there are numerous factors that influence the chloride content of sweat.[7] It is possible to increase the chloride by increasing the skin temperature. The salt

TABLE III. COMPARISON OF RESULTS FROM FOUR DIFFERENT STUDIES ON SWEAT CHLORIDE (MEQ./L.)

INVESTIGATOR	CONTROLS			ALLERGIC PATIENTS		
	NO.	MEAN	MEDIAN	NO.	MEAN	MEDIAN
1. Hsia et al.	83	19.5	—	31	38.6	—
2. Kulczycki et al.	39	21.6	—	31	19.8	—
3. Van Metre et al.	64	23	18	47	18	14
4. Our study	70	35	34	55	46	35

content in sweat is greater in winter than in summer. When sweating occurs, the rate and duration influence the salt content. Other factors are diet, presence of fever, dehydration, state of renal and adrenal function, and malnutrition.

In a study by Johnson and associates,[8] it was found that the three primary factors concerned with the concentration of chloride in sweat are: (1) skin temperature, (2) rectal temperature and rate of sweating, and (3) individual idiosynerasies.

Gochberg and Cooke[9] suggest that the abnormality in sweat in cystic fibrosis of the pancreas may result from an alteration in the quantity of energy available for secretion. Thus, when readily available energy is limited, there may be a rise in concentration of solute.

SUMMARY

The concentration of chloride in the sweat of allergic children was compared with the concentration of this electrolyte in 70 normal children who were used as controls. The mean concentrations of chloride in the experimental and control groups were both within the normal physiologic range, and no significant differences were found. An unexplained variation in concentration of sweat chloride was observed in male and female children at different age periods.

Dr. Roselyn P. Epps gave helpful advice during the progress of this study. Dr. Robert L. Baird and Miss Louise A. Covington were helpful in securing patients. Technical assistance was provided by Mr. James A. Ross, Mr. Andrew Jackson, Miss Mary E. Allen, and Miss Eve Hossfeld.

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SERUM SICKNESS

II. Demonstration and Characteristics of Antibodies

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With the advent of antibiotic therapy and the widespread development of active immunization programs, the use of commercially prepared products made from foreign sera has greatly diminished. Anti-pneumococcal serum is rarely, if ever, administered. Diphtheria antitoxin, botulin antitoxin, gas gangrene antitoxin, anti-snake venom serum, and, more recently, anti-rabies horse serum and experimental anti-cancer horse serum are used only in infrequent situations. The most commonly used remaining product in this group is tetanus antitoxin.

Tetanus antitoxin is still widely administered for passive protection in nonimmunized individuals. Despite its purification, serum sickness reactions occur and may be quite serious. Recently, Toogood[1] estimated that 136,000 doses of tetanus antitoxin are administered yearly in Canada, resulting in about 7,900 severe allergic reactions, an incidence of 5.3 per cent. Other estimates have ranged from 1.6 to 20 per cent.[2, 3] In our own experience, allergic reactions occur approximately in the same proportion as reported by Toogood.

Serum sickness is not always a self-limiting, innocuous illness. Unusual reactions which have occurred include brachial plexus neuritis, myocarditis, encephalitis, and the Guillian-Barré syndrome.[4-6]

We have previously described the application of the tanned cell hemagglutination test to the demonstration of antibodies to horse serum.[7] Using this very sensitive serologic technique, we found high titers of horse serum antibodies in the sera of all patients who developed serum sickness. The antibodies frequently persisted at high levels for many months or years after all symptoms had disappeared. More significantly, patients who had a hemagglutination titer of 160 or more prior to the injection of tetanus antitoxin developed serum sickness.

In addition to the precipitating antibody which appears to play the major role in the tanned cell hemagglutination test, anaphylactic[8] and skin-sensitizing[9]

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antibodies have been reported to occur in serum disease. In order to study further the basic immunologic mechanisms involved in serum sickness, we undertook a comparative study of the several antibodies in their relationship to the clinical manifestations of the disease. We also carried out further studies of the regular application of hemagglutination methods for predicting the development of serum sickness or for differentiating it from clinically similar disease states. Our findings are contained in the following report.

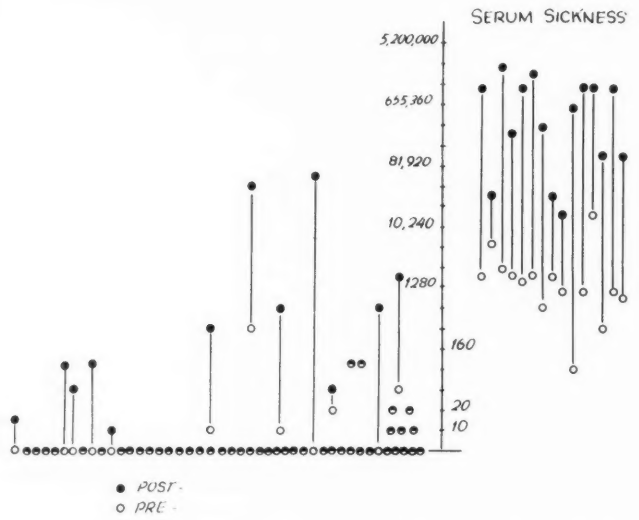

Fig. 1.—Pre- and post-T.A.T. hemagglutination titers of asymptomatic patients and those with serum sickness.

METHODS AND MATERIALS

Blood samples were obtained from patients treated in the Emergency Room of the Buffalo General Hospital prior to the administration of 1,500 units of tetanus antitoxin (T.A.T.) and again 10 to 14 days later. If symptoms of serum disease occurred, patients were instructed to return immediately. Clinical observations and serologic studies were carried out during and following the symptomatic period.

Antitoxin was given only if a preliminary intradermal skin test with 0.1 c.c. of a 1 : 10 dilution was negative.

RESULTS

Tanned Cell Hemagglutination.—The adaptation of the tanned cell hemagglutination test to the study of serum sickness has already been described in detail.[7] Since the initial report, our experience has been significantly increased.

Human group O Rh negative red blood cells were treated with dilute tannic acid and coated with horse serum. These cells were added to the patients' sera prepared in serial dilutions. The patterns were read after standing at room temperature for 2 hours, and again after incubation in the icebox overnight.

Serum samples, drawn before and after injection of T.A.T. (pre- and post-T.A.T.) were obtained from 71 patients, of whom 15 developed serum sickness (Fig. 1).

All patients with serum sickness had a titer ranging between 10,000 and 1,000,000. Only 2 patients of the 56 without serum disease fell in this range. Fourteen of the 15 patients who subsequently developed symptoms had a hemagglutination titer over 200 prior to the administration of T.A.T. Only 1 patient who remained asymptomatic was in this range.

Post-T.A.T. samples only were obtained from 48 other patients, of whom 25 had serum sickness (Fig. 2). All 25 had titers above 10,000. The titers of the 23 asymptomatic patients were all well below this level.

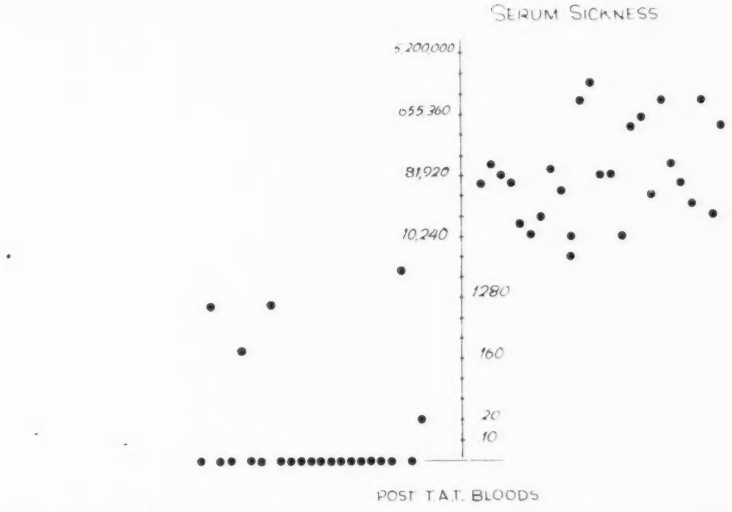

Fig. 2.—Post-T.A.T. hemagglutination titers of asymptomatic and serum sickness patients from whom pre-T.A.T. serum was unavailable.

Hemagglutination titers were also measured in 19 patients who had preliminary positive skin tests and, therefore, were not given antitoxin. These titers ranged from 0 to over 4,000. Table I summarizes the relationship between hemagglutination titers and skin test reactivity. Also included in the table are determinations on the sera of 58 healthy blood donors. Four of this group had titers above 100.

TABLE I. THE RELATIONSHIP OF PRE-TREATMENT HEMAGGLUTINATION TITERS TO SKIN REACTIVITY AND THE RANGE OF HEMAGGLUTINATION TITERS IN RANDOMLY SELECTED RED CROSS SERA

HEMAGGLUTINATION TITERS	BLOOD DONORS	PATIENTS		
		SKIN TEST NEGATIVE	SKIN TEST POSITIVE	TOTAL
0-100	54	113	8	175
100-200	1	1	1	3
200-500		8		8
500-1,000		3	1	4
1,000-2,000	1	6	3	10
2,000-4,000	2	7	3	12
Over 4,000		2	3	5
				217

Agglutination With Inert Particles.—The tanned cell hemagglutination test requires several hours to perform. A more rapid test which could be used in conjunction with skin testing in the average hospital emergency room might serve a greater need. In searching for such a test which might accurately predict which patients would be likely to develop serum disease, experiments with latex and bentonite particles were performed. These particles can be coated with horse serum and made available for immediate use.

A 10 per cent suspension of polystyrene latex particles,* 0.814 micron in diameter, was made in distilled water. It was filtered through No. 404 S & S† paper† to remove any large particles and the filtrate was diluted 1:100 with glycine buffer,‡ pH 8.2. Horse serum in varying dilutions was used to coat the latex. One-tenth of a milliliter of the coated latex particles and 0.1 ml. of antisera in serial dilutions were incubated for 30 minutes at 37° C. Following centrifugation for one minute, any agglutination was observed.

Bentonite agglutination tests were performed by Dr. John Bosevitch of the National Institutes of Health.

Both bentonite and latex particles could be agglutinated by serum sickness antisera which had high hemagglutination titers. However, weaker sera were unable to cause agglutination. With latex particles, 8 sera were tested. Five were positive and the titers ranged between 1:10 and 1:250. These sera all had hemagglutination titers above 40,000. The three negative sera had hemagglutination titers of 400, 1,000, and 20,000.

Using bentonite, positive reactions were obtained with four sera which had hemagglutination titers ranging from 40,000 to 1,000,000. The titers against bentonite ranged from 1:128 to over 1:2000. Two sera with hemagglutination titers of 2,000 and 16,000 did not agglutinate bentonite particles.

Hemagglutination With Formalized Cells.—Formalin-treated red blood cells have been shown to be very stable[10] and, therefore, possibly adaptable for a rapid test. Formalized cells§ were treated with tannic acid and coated with horse serum in the same manner as previously described. Hemagglutination experiments were then performed at various time intervals following the initial preparation of these cells.

Formalized rabbit red blood cells were found to be useful for demonstration of the hemagglutination reaction. Furthermore, these coated formalized cells remained stable for at least 6 weeks following their preparation. The results of experiments comparing 6-week-old sensitized formalized red cells with freshly prepared O negative red cells are shown in Table II.

Experiments with formalized red blood cells obtained from sheep, beef, chicken, and human sources were also done. These titers were not as high as those obtained with rabbit cells.

*Dow Corporation.

†Schleicher and Schuell Co., Inc., New York, N. Y.

‡975 ml. of 0.1M glycine and 2.5 ml. of 1N NaOH were made up to 1,000 ml. with distilled water. The pH was adjusted to 8.2. Ten grams of NaCl was then added.

§Obtained through the courtesy of Difco Laboratories, Detroit, Mich.

Passive Cutaneous Anaphylaxis.—As a convenient mode of demonstration of the anaphylactic antibody, the passive cutaneous anaphylaxis (PCA) reaction, as described by Ovary,[11] was employed. One-tenth of a milliliter of patient's serum, in varying dilutions, was injected intradermally in the back of a 250 gram albino guinea pig. Six hours later, 1.0 ml. of antigen solution consisting of equal parts of horse serum (diluted 1 : 10 in normal saline) and Evans blue dye was injected intravenously in the hind foot. After 30 minutes, the animal was sacrificed and the size and intensity of any reaction found on the innerside of the skin was recorded. The results, compared with the hemagglutination titers of the same sera, are shown in Fig. 3.

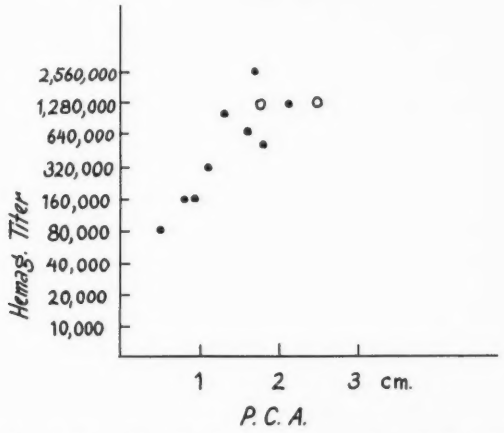

Fig. 3.—Comparison of the size of passive cutaneous anaphylaxis reactions with the corresponding tanned cell hemagglutination titers of serum sickness sera. Closed circles indicate human serum disease antisera; open circles are anti-horse serum rabbit serum.

Of 15 serum sickness sera tested, 9 reacted positively by this method. Titers ranged between 1 : 100 to over 1 : 400. There appeared to be a correlation between the level of the hemagglutination titer and the PCA reaction. All 9 PCA positive antisera had hemagglutination titers above 80,000. The 6 negative sera were all below this titer. In addition, the actual size of the PCA reaction correlated with the level of the hemagglutination titer.

TABLE II. COMPARATIVE HEMAGGLUTINATION TITERS OF FORMALIZED RABBIT RED BLOOD CELLS PREPARED 6 WEEKS PREVIOUSLY AND FRESHLY COATED HUMAN RED BLOOD CELLS

PATIENT	FORMALIZED CELLS (RABBIT)	UNTREATED CELLS (HUMAN)
E. R.	320	640
H. W.	80	160
B. L.	160	320
S. C.	320	320
E. S.	80	40
F. S.	160,000	160,000
C. S.	100,000	100,000
L. N.	200,000	800,000
P. K.	0	0
W. V.	0	0
P. F.	0	0
A. B.	40	0
Rabbit No. 64	400,000	1,600,000

Complement Fixation.—Having demonstrated anaphylactic and hemagglutination reactions, we next studied the complement fixing properties of serum sickness sera.

Sera were inactivated at 56° C. for 30 minutes. Tests were performed by mixing 0.1 ml. each of dilutions of antiserum and antigen with 0.1 ml. of an appropriate dilution of guinea pig serum containing about two full units of complement. The tubes were shaken and incubated at 4° C. for 2 hours and 37° C. for 1 hour. Two-tenths of a milliliter of sensitized sheep cells consisting of equal parts of 4 per cent washed sheep red blood cells and rabbit serum containing 2 minimum hemolytic doses of sheep cell hemolysin was added. The mixtures were re-incubated at 37° C. Readings were taken 15 minutes, 1 hour, and 2 hours after addition of the sensitized cells.

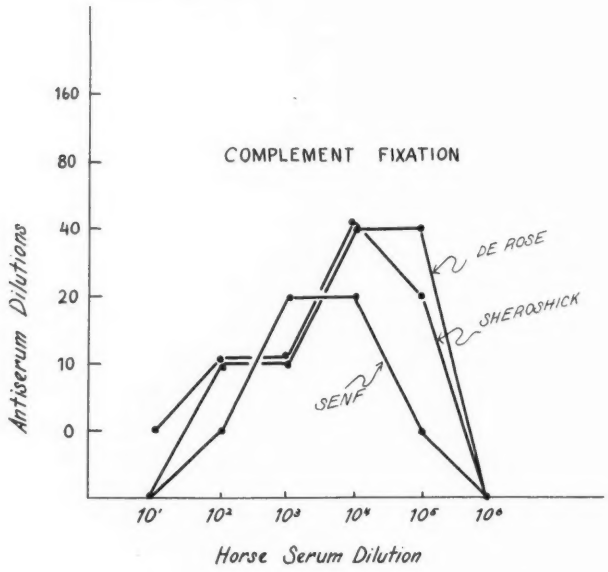

Fig. 4.—Complement fixation curves of 3 serum sickness antisera. Tanned cell hemagglutination titers of all 3 antisera were over 1,000,000.

Complement fixation reactions were positive in 8 of 15 sera tested. These complement fixing sera all had hemagglutination titers above 100,000.

Complete complement fixation curves were obtained for 3 antisera and are presented in Fig. 4. Typical strong reactions were found with marked inhibition in areas of antigen excess.

Passive Transfer.—An interesting feature of serum disease, described many years ago, is the presence of a transitory skin-sensitizing antibody.[9] Our interests were particularly concerned with the time of appearance and disappearance of this reagin in comparison with the tanned cell hemagglutination reaction on one hand and clinical symptoms on the other.

Passive transfer studies were performed in the usual manner. One-tenth of a milliliter of sterile antisera was injected intradermally in nonsensitive

recipients. Forty-eight hours later the sensitized sites were challenged with 0.05 ml. of horse serum diluted 1:10.

Previously, 14 of 22 serum sickness antisera were reported to give positive reactions.[7] These sera were obtained at varying intervals following the clinical symptomatology. Eight new sera from patients with acute symptoms were tested and all contained skin-sensitizing (P.K.) antibodies.

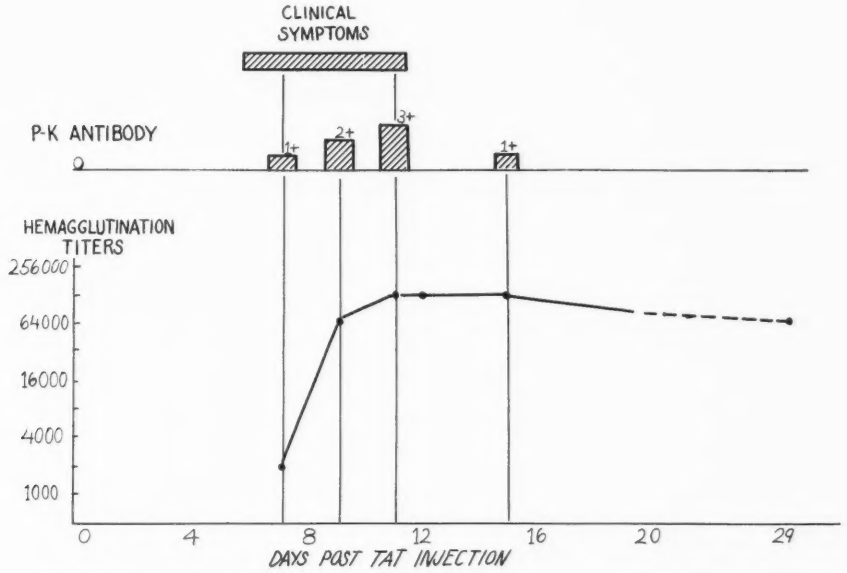

Fig. 5.—Relationship of the time of clinical symptoms, occurrence of the skin-sensitizing antibody, and the tanned cell hemagglutination titer. (Patient W. C.)

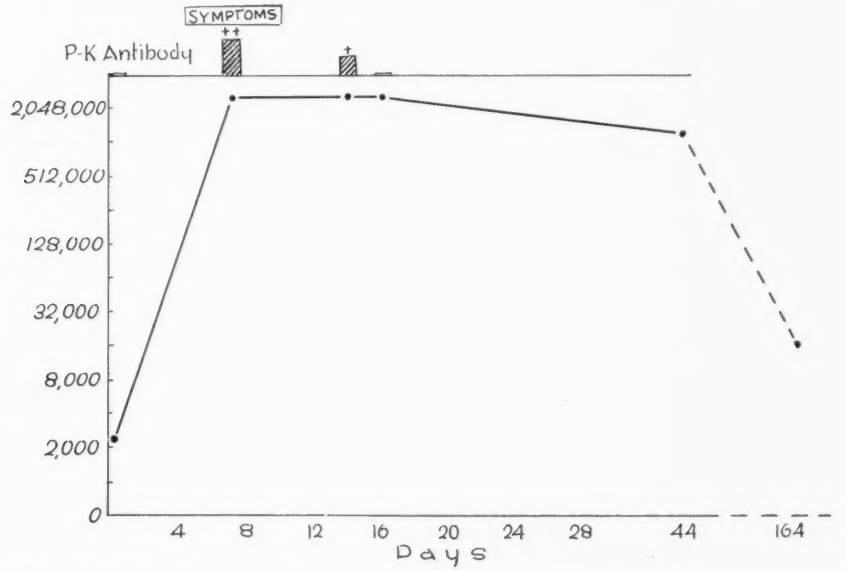

Fig. 6.—Relationship of the time of clinical symptoms, occurrence of the skin-sensitizing antibody, and the tanned cell hemagglutination titer. (Patient C. D.)

More complete studies were done with successive antisera of 2 patients (Figs. 5 and 6). The P.K. antibody apparently appeared concomitantly with the onset of clinical symptoms, and seemed to precede the rise of the hemagglutination titer. It also disappeared rapidly in contrast to the lingering high hemagglutinating antibody. Similar results have been previously reported in a case of serum disease following bovine T.A.T.[12]

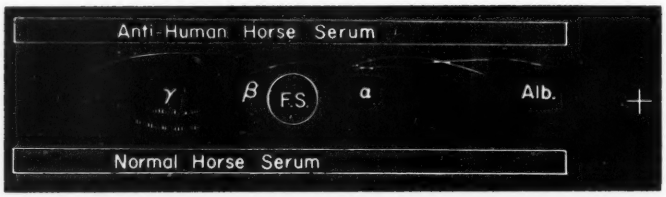

Fig. 7.—Immunoelectrophoresis: Following electrophoresis of patient's serum, normal horse serum was added in one adjacent trough and anti-human serum horse serum in the other. An arc of precipitate formed between horse serum and a component of human antiserum with a migration of gamma globulin.

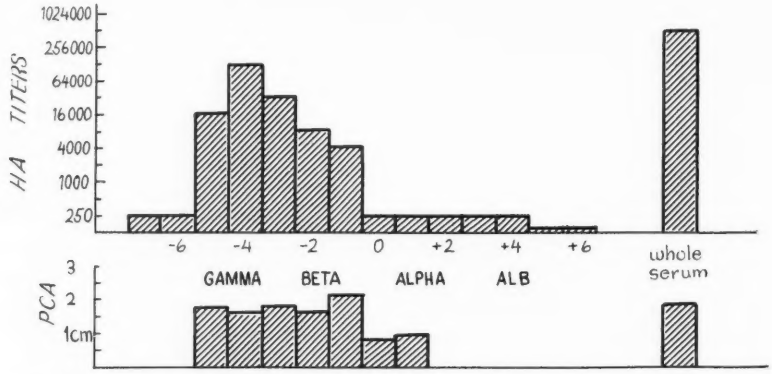

Fig. 8.—Comparison of the hemagglutination titer and size of the PCA reaction of electrophoretically separated fractions of human antiserum. (Patient W. S.)

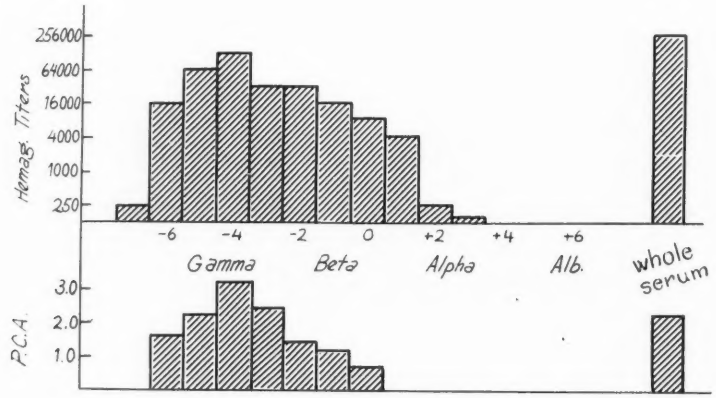

Fig. 9.—Comparison of the hemagglutination titer and size of the PCA reaction of electrophoretically separated fractions of human antiserum. (Patient L. N.)

Electrophoretic Mobility.—

A. Precipitating antibody: The precipitation reaction is the classical immunologic procedure associated with serum disease.[13]

Immunoelectrophoresis of patients' sera was performed to determine the location of the precipitating antibody. Following electrophoresis of antiserum in 1 per cent agar (pH 8.2, ionic strength 0.025), horse serum was added in an adjacent longitudinal trough. As an indicator, anti-human serum horse serum was added in the other trough. The plate was observed daily and any precipitation ares recorded.

An arc of precipitate formed between horse serum and a component of antiserum with the migration rate of a gamma globulin (Fig. 7). This result was found with all three antisera tested.

B. Hemagglutinating antibody and anaphylactic antibody: Antiserum was fractionated by means of agar electrophoresis. Following completion of the electrophoretic separation, the agar was cut into fifteen 1 cm. strips which were frozen and later thawed. These fractions were numbered from 0 at the center well to +7 at the anode and –7 at the cathode. The hemagglutination titer and PCA reaction of each fraction were determined. The results obtained with two typical sera are illustrated in Figs. 8 and 9.

In all sera tested, the hemagglutinating and anaphylactic antibodies were located in the gamma globulin fraction. There was a good correlation between the hemagglutination titer and the size of the PCA reaction of each individual fraction.

DISCUSSION

Further experience with the adaptation of the tanned cell hemagglutination test to the study of serum disease has confirmed the initial conclusions. The pre-T.A.T. titer may prove useful in predicting who will develop primary or accelerated serum disease if given prophylactic antitoxin. The post-T.A.T. titer may be useful in supporting the diagnosis of clinical serum disease. The hemagglutination test itself is relatively easy to perform and is practically adaptable to the average hospital serologic laboratory. However, it usually requires several hours or a day to perform.

Inert particles of latex and bentonite proved less sensitive than red blood cells in demonstrating agglutination. Particularly, the elevated hemagglutination titers found in the pre-T.A.T. serum of patients subsequently developing serum disease could not be demonstrated. Thus, as a rapid practical test for predicting possible serum reactions, inert particles were now useful.

However, tests with formalized cells coated with horse serum proved very successful. These cells, which can remain stable for long periods of time, may fill the need for a rapid procedure. A slide agglutination technique with formalized cells is now under study.

The patients with elevated titers prior to antitoxin administration had no history of serum disease or known exposure to products made from horse serum. Therefore, the initial stimulus for antibody production remains open to speculation.

Tanned cell hemagglutination is recognized as a very sensitive method of measuring antigen-antibody reactions. There is some evidence that other immunologic reactions may be dependent upon the same or partially identical antibody or antibodies. In a previous communication,[7] direct precipitation reactions, long the classical immunologic trademark of serum disease, were reported. In general, those antisera containing precipitins had high hemagglutination titers. Further immunoelectrophoretic studies revealed that only those antisera with hemagglutination titers above 100,000 showed precipitate ares with components of the horse serum antigen. The time relationship of the precipitation and hemagglutination reactions to the clinical symptoms of serum disease are also comparable. It has long been observed that precipitins are first noted about 3 to 4 days after the onset of the illness and may persist for a short time following recovery.[5, 14] Loveless[15] carried out quantitative measurements of precipitable antibody nitrogen and found the maximum amount on the fourteenth day post-T.A.T. Studies of experimental serum disease in rabbits have also shown a similar time relationship of the precipitin antibody to the clinical symptoms.[16] Serial studies of the hemagglutination titers in several patients have revealed the same time pattern. The titer rose after the onset of symptoms and often reached its peak following the patient's recovery. The antibody, however, is detectable by this method for an indefinite period after the symptomatology subsides.

Good correlation of the complement fixation and the passive cutaneous anaphylaxis reaction with the level of the hemagglutination titer was found. Comparable results were also obtained by hemagglutination and PCA with electrophoretically separated fractions of antisera.

The immunologic characteristics of the artificially produced skin-sensitizing antibody and its difference from the naturally occurring reagin were thoroughly studied by Cooke and his associates.[17] When compared to the spontaneous skin-sensitizing antibody, these authors found the induced antibody to have more specificity, usually a lower titer, and be less thermolabile. It is primarily gamma globulin, and its activity is more easily recovered following electrophoretic fractionation of the serum.

Comparison of the presence of horse serum reagin and the level of the hemagglutinating antibody titer indicates a lack of correlation between the two. This is further confirmed by the different time appearance of each. The distinction between the skin-sensitizing antibody and the precipitin and anaphylactin occurring in serum disease has been pointed out by several investigators. Tuft and Ramsdell,[18] in 1929, differentiated the antibody responsible for the P.K. reaction from the anaphylactic antibody on the basis of the independent occurrence of each. Karelitz and Glorig,[19] studying the experimental production of "passive serum sickness," confirmed the lack of correlation of the precipitin and the skin-sensitizing antibody. In 1947, Loveless[15] showed that the skin-sensitizing antibody remained following removal of precipitins from a serum sickness antisera. Thus it would seem that there are probably at least two distinct types of antibodies produced with serum disease.

Studies of the naturally occurring ragweed reagin and the ragweed hemagglutinating antibody have not fully resolved the question of identity. Gordon, Rose, and Sehon[20] reported the skin-sensitizing antibody titer and hemagglutination titer to "run somewhat parallel." The skin-sensitizing antibody was found to be completely absorbed out by the sensitized red cells in the hemagglutination reaction. Similar findings of the absorption of grass skin-sensitizing antibodies by the hemagglutination reaction of red cells linked to grass pollen extract with patient's serum were also reported.[21] However, studies from this laboratory have shown no correlation of ragweed reagin and ragweed hemagglutinating antibody titers.[22] High hemagglutinating antibody titers have been found in the presence of low reagin titers and vice versa. In addition, these two titers react independently following treatment of either conventional or repository type.[24]

Although their skin-sensitizing antibody is demonstrable by passive transfer for only a brief period, patients have a positive direct skin test to horse serum for a long time following serum disease. Longcope and Rackemann,[5] in 1919, pointed out that skin reactions remained positive for "as long as patients" could be observed. Also, in some patients, direct skin reactions became positive but attempts to transfer the reagin passively with acute antisera have failed. This difference is probably related to a quantitative difference in sensitivity of direct and indirect skin tests.

Studies of experimental serum sickness in animals have indicated that soluble antigen-antibody complexes are formed in antigen excess and deposited in blood vessel walls, resulting in the clinical symptoms and pathologic changes of serum disease.[16] A similar mechanism may prevail in man. The rising titer of hemagglutinating antibody as the patient is recovering from the disease tends to bear out this supposition. However, the appearance of a passive transfer antibody concomitantly with the onset of clinical symptoms of serum disease is unexplained. It could be a more important immunologic etiological factor in primary serum sickness than has been previously generally recognized. It certainly has been implicated in the atopic or anaphylactic reactions which occur immediately following horse serum administration. The question must still remain unsettled at present.

Positive heterophile reactions have been reported to occur with acute serum sickness sera.[24] Absorption with guinea pig kidney or sheep cells inhibits the reaction in contrast to the findings with infectious mononucleosis antisera. Pre- and post-T.A.T. sera from 4 patients who developed serum sickness were tested. Three of these 4 patients had negative heterophile titers in both paired sera. Only 1 patient developed a positive heterophile titer with serum disease. The use of refined antitoxin rather than crude horse serum may be the explanation for this failure of stimulation of heterophile antibodies.

Antigen fractionation studies and the antigenic role of the flocculating antitoxin itself will be the subjects of a subsequent report.

SUMMARY AND CONCLUSIONS

1. With a high degree of accuracy, the tanned cell hemagglutination test can (a) predict which patients are likely to develop primary serum sickness if given T.A.T. and (b) can verify or establish the clinical diagnosis of serum disease.

2. Positive complement fixation and passive cutaneous anaphylaxis reactions were obtained with a majority of acute serum disease sera. A good correlation was found between the level of the hemagglutination titer and the presence of positive precipitation, PCA, and complement fixation reactions. Furthermore, the hemagglutinating, precipitating, and anaphylactic activity of serum sickness antisera resides in the same serum components.

3. An artificially induced transient skin-sensitizing antibody is found with serum disease. It apparently is different from the hemagglutinating or precipitating antibody. Its role in serum disease is still not clear.

4. Formalized red cells, which are treated with tannic acid and coated with horse serum, remain stable for a long period of time and therefore are adaptable for a rapid hemagglutination test. Inert particles of latex or bentonite are less sensitive than red cells in demonstrating agglutination reactions.

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EDITORIAL

Clinical Papers for the Journal—Write and Wrong

THE paucity of clinical papers in the JOURNAL OF ALLERGY has led to an opinion, sometimes expressed, that the JOURNAL is exclusively interested in the results of laboratory investigation. However, this is not the desire of the Editorial Board which would like to see a better balance but feels that certain obstacles stand in the way of achieving it. Within the past year the Board decided that its point of view should be placed before the readers of the JOURNAL by the Editor. The Editor cannot pretend to present the Board's view in entirely undistorted form but has attempted as best he can to do so in what follows.

There is ample evidence in the literature to indicate that clinical allergy has presented an exceptionally difficult challenge to those who would put their observations and ideas in print. The diseases encompassed within the field are for the most part poorly understood and complex in nature. The terminology is far from unambiguous and there is a tendency, like Humpty Dumpty, to exact from words the meaning that fits the occasion. It is among the clinical contributions that this lack of definition and precision most often seems to have undermined the will to adhere strictly to the principles of logical thought and especially to have fostered the easy error of *post hoc ergo propter hoc.*

Without doubt the division of scientific papers into stereotyped sections will cramp one's literary style but such a division also greatly simplifies the task of presentation, especially the very essential division between observation and the interpretation placed on what was observed. The following sentence, of a type commonly encountered, will illustrate this point—"All the allergic manifestations were relieved by elimination of wheat from the diet." This might seem a simple observation and such a statement is usually so intended. But assumptions and interpretation are woven through it. What were the manifestations and what was the evidence that they were allergic in nature? Was elimination of wheat alone responsible for the observed relief and what steps were taken to rule out other factors? To what extent was elimination of wheat achieved and how was this done? Thus "observation" needs to be disentangled from "interpretation" in the words "allergic," "relieved by" and "eliminated." Obsessive insistence on this separation is a good fault.

Clinical impressions are often the first step toward the recognition of important facts but such impressions should be put to the test by well thought out experiment. In the field of therapy, elimination of bias in patient and physician is often necessary before a useful and correct conclusion can be reached. A successful and common way of doing this is the "double blind" experiment. However, the means adopted to establish and maintain this kind of experimental control are of the utmost importance and will need to be described in detail if the skeptical reader is to accept such study as adequately controlled. There is a large backlog of clinical impressions waiting for confirmation by experiment and many of our dearest dictums need to be put to the test. Where is one to find solid evidence in support of the practice of using iodides as expectorants; or to show that atropine and, more recently, the antihistaminic drugs are contraindicated in asthma; or that patients with hay fever, if not treated with injections of allergenic extracts, will develop asthma? The list can be extended. Our patients and our specialty will be poorly served if we enlarge the backlog with complacent indifference. To establish or dispel will require much time and effort but these will be spent in the best of interests and the reward will be lasting.

F. C. L.

OBITUARY

M. J. GUTMANN

M. J. GUTMANN died on June 13, 1961, in Jerusalem, Israel. Dr. Gutmann was born in Heidenheim, a small town in Southern Germany, on March 19, 1894. He studied medicine at various German Universities, including Heidelberg. During World War I he served as a noncommissioned officer in the Medical Corps. In 1920 he received his medical degree at the University of Munich; his dissertation dealt with hereditary diseases among Jews.

Dr. Gutmann's immediate postgraduate training and research were carried out at the Psychiatric Research Institute of the University of Munich. Later his interest turned to the field of tuberculosis and he wrote the monograph *Die Lungentuberkulose in dem Allgemeinen Praxis* (Munich, 1926).

During 1927-1928, Dr. Gutmann attended Storm van Leuwen's allergy clinic at the University of Leyden (Holland) and since then he was almost entirely involved in the practice and research of allergy. He was one of the pioneer allergologists in Germany and headed its first allergy department in a hospital. He was co-author of an excellent booklet on pollenosis *Die Pollenallergie* (Munich, 1929), and wrote a general review of allergic diseases *Von Asthma, dem Heufieber, dem Juckreiz, der Migraene und anderen Allergischen Krankheiten* (Munich, 1934).

After the Nazi regime came to power, Dr. Gutmann settled in Jerusalem and opened his office for the practice of allergy, the first in this part of the world. He was soon appointed allergy consultant to the Rothschield-Hadassah-University Hospital. His extensive practice, keen interest in his patients and in the various aspects of allergy, urged him to continue his study and research of various ethnologic groups in new social, economic, and climatic surroundings. In his own office, without any financial support or grants, aided only by his loving wife, he compiled his observations in the monograph *Heredity and Environment as the Cause of Allergic Disease: Allergy Studies in Israel (1959).* This is an excellent example of a single man's devotion and contribution.

In his lifetime Dr. Gutmann published over 120 scientific monographs and papers. His early works dealt with heredity, tuberculosis and psychiatry; the majority of the later publications cover various aspects of allergy, applied immunology, and related fields.

Dr. Gutmann took great interest in the activities of the Israel Medical Association and for many years was chairman of its Committee on Nutrition. He was a member of the Israel Society of Genetics.

Dr. Gutmann was rightfully considered the dean of allergologists in Israel. When he founded the Israel Society of Allergy he was elected its first president and held this office until his death. He was a Fellow of the founding group of the International Association of Allergology and was repeatedly sent as national delegate to its House of Delegates. In 1958 the House elected him to the executive committee of I.A.A.

Dr. Gutmann was a Fellow of the American College of Allergists, Associate-Fellow of the American Academy of Allergy, a Corresponding Member of the French Allergy Society, and an Honorary Member of the Argentine Allergy Society. He participated in the Collegium Internationale Allergologicum and was a Contributing Editor of the International Archives of Allergy and Applied Immunology.

Dr. Gutmann is survived by his charming wife, Kathryn, two sons, Dr. Emanuel Gutmann, lecturer in Sociology at the Hebrew University of Jerusalem and Dr. Joel Gutmann (Gat) Senior Scientist (Chemistry) at the Weizmann Institute of Science, Rehovoth, and three grandchildren.

Dr. I. Glazer

ANNOUNCEMENTS

Israel Society of Allergology

The Executive Committee of the Israel Society of Allergology for the period 1961-1962 is as follows.

President: N. Lass, M.D., Tel-Aviv.
Secretary: I. Glazer, M.D., Tel-Aviv.
Treasurer: M. Brochow, M.D., Tel-Aviv.
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Denver-Hilton Hotel, Denver, Colorado
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The Journal of

Official Organ of AMERICAN ACADEMY OF ALLERGY

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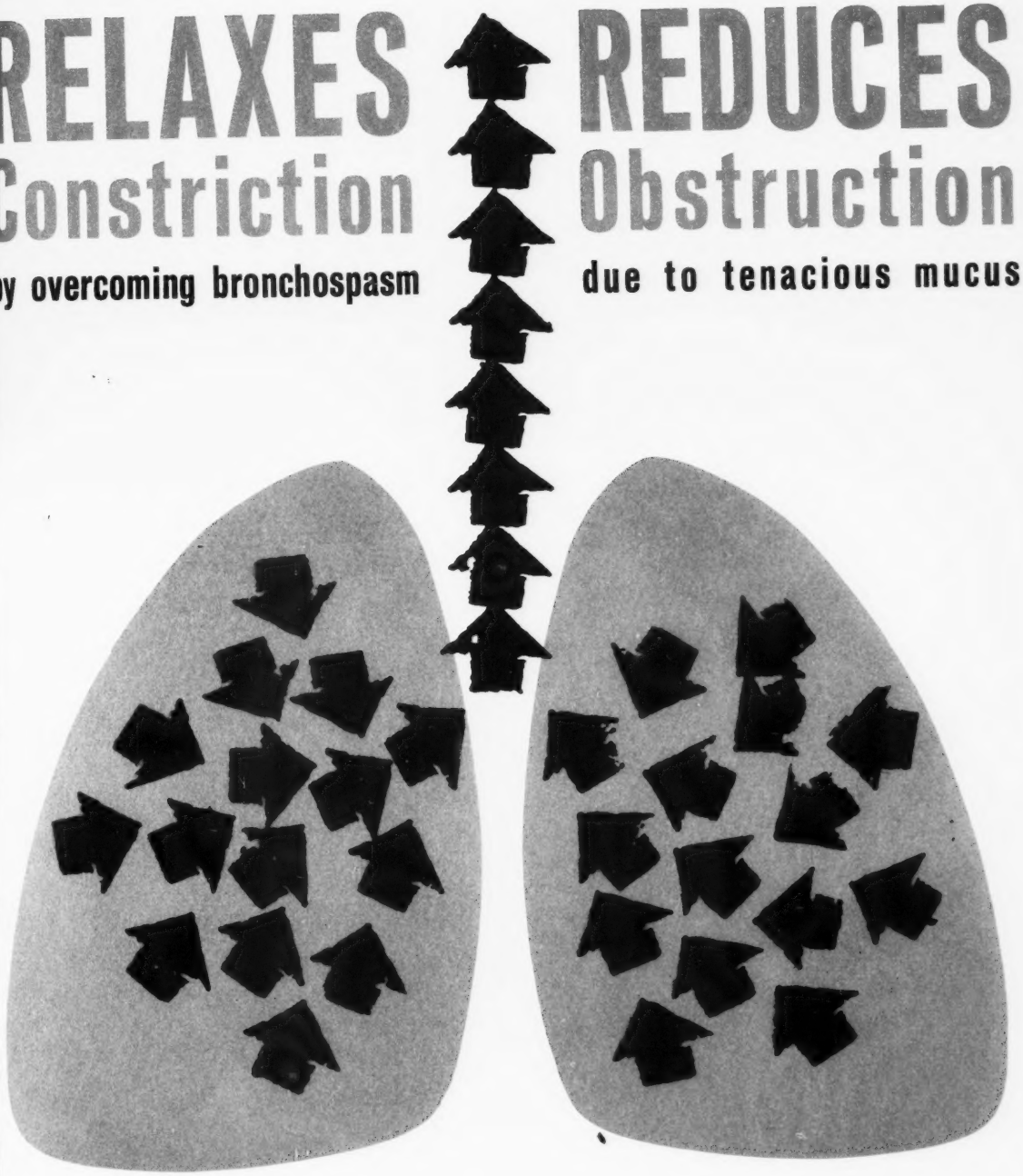

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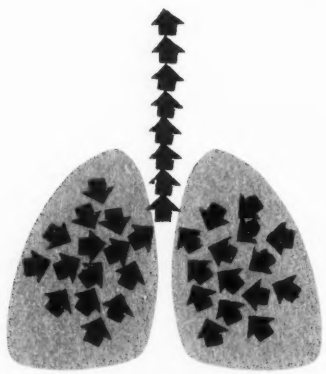

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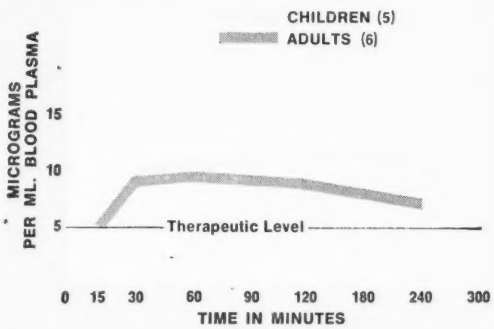

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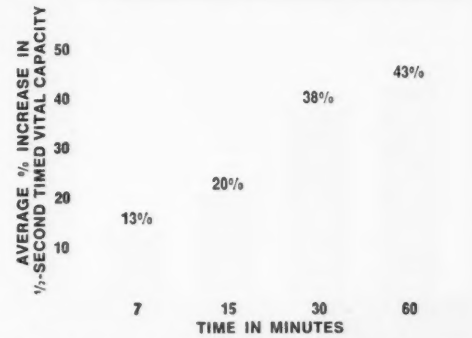

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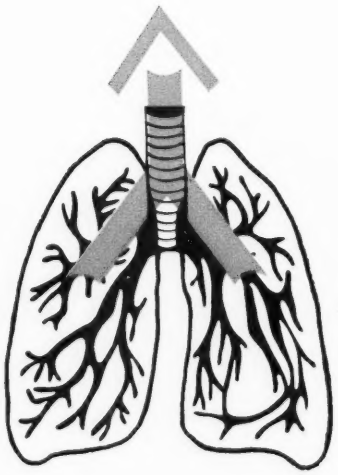

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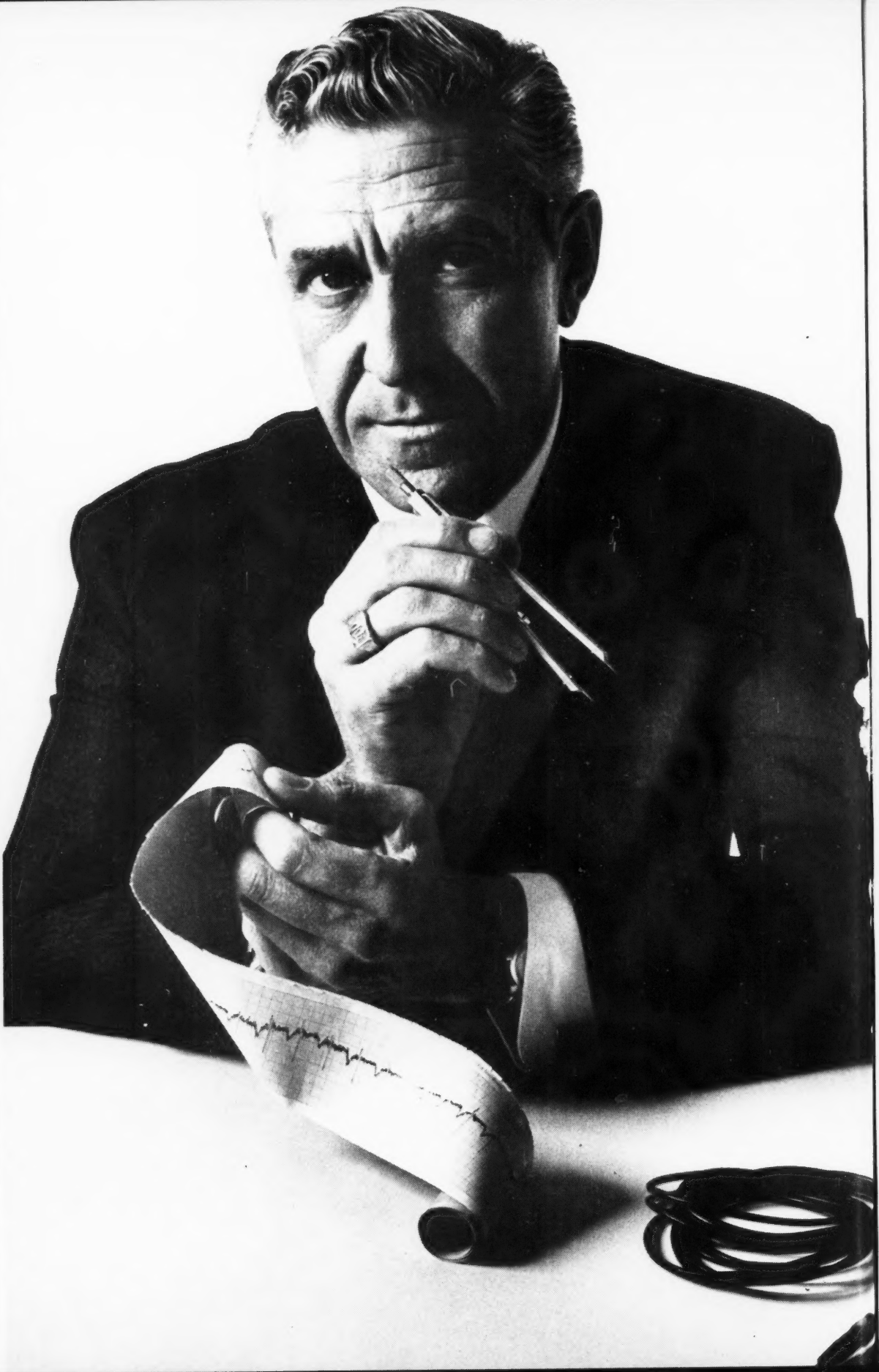

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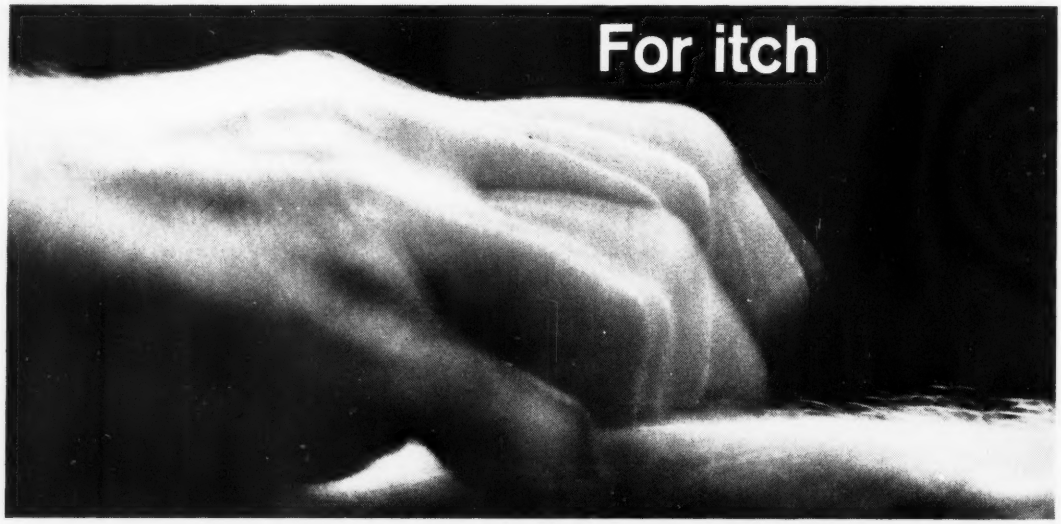
For allergy



Everyday practice report:
Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 4026 cases have now been analyzed. In 2260 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

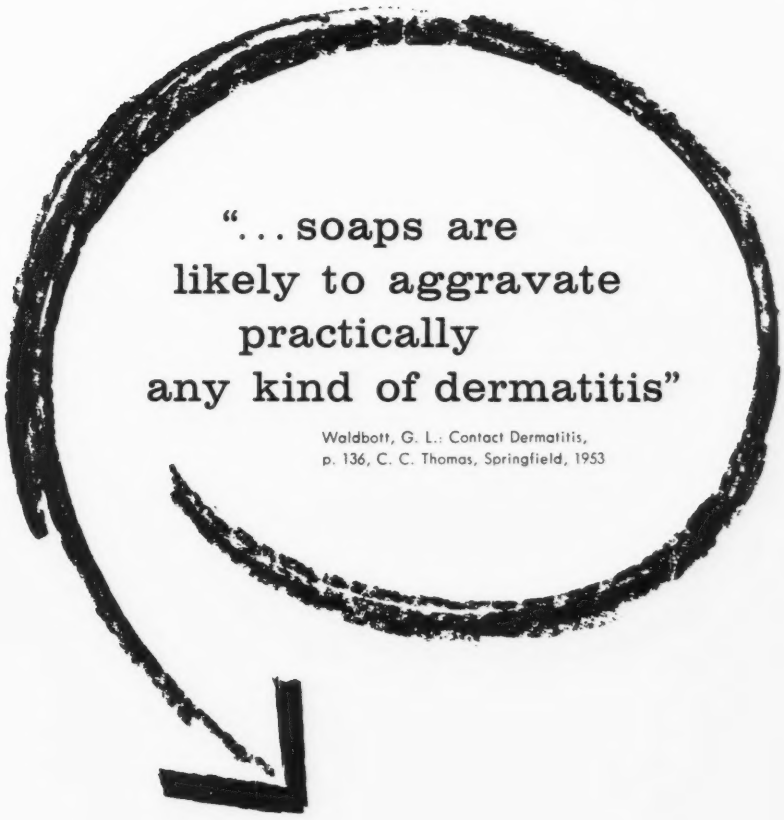
FORHISTAL® maleate
(dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

CIBA
SUMMIT, NEW JERSEY

Forhistal®
rated better than previous therapy in 7 cases out of 10

Forhistal Lontabs® for greater convenience, smoother response, prolonged action.

2/2910MK-2



AVEENO®-BAR

for soap-free cleansing

Aveeno-Bar is a richly-lathering soap-free cleansing bar that contains more than 50% soothing colloidal oatmeal. It is particularly well-suited to cleansing sensitive atopic skin.

It contains no soap whatsoever, and, unlike soap, contains no fatty acids which may aggravate an already irritated condition. Aveeno-Bar has a pH of 5.7 to approximate the normal pH of skin. It lathers richly even in the hardest water.

Active Ingredients: Aveeno Colloidal Oatmeal; special blend of sudsing agents; dewaxed hypo-allergenic lanolin; hexachlorophene.

AVEENO CORPORATION 250 WEST 57TH STREET NEW YORK 19, N. Y.

CAUTION

ATOPIC SKIN • TREAT GENTLY!

FOR THE ACUTE STAGE

"The bath I use most commonly is Aveeno"[1]

AVEENO®
Colloidal Oatmeal
for **Soothing Colloid Baths**

Aveeno Colloidal Oatmeal baths have found a secure place in the therapeutic art of managing the atopic skin. They are "basic wet therapy"[2] for acute, weeping, inflamed and itching stages of infantile eczema—they are soothing, eminently safe, antipruritic and anti-inflammatory.

Available in 18 oz. and 4 lb. boxes

FOR THE CHRONIC, DRY STAGE

"If the skin is dry, a miscible, oily preparation is added to the bath."[3]

AVEENO® OILATED
for **Colloidal *Emollient* Baths**

Aveeno Oilated baths are specific for the drier and more chronic, lichenified stages of atopic dermatitis. They provide soothing, antipruritic and anti-inflammatory Aveeno Colloidal Oatmeal saturated with 35% emollient oils.

Available in 10 oz. cans

References: 1.Epstein, N. N.: Eczema, Allergic, in Infants and Children (Atopic Dermatitis) : in Current Therapy, 1960. 2. Senear, F. E., and Haeberlin, J. B., Jr.: M. Clin. North America, March 1958. 3. Brunsting, L. A.: Postgrad. Med. 26:431, 1959.

Aveeno Corporation 250 West 57th Street New York 19, N. Y.

Pioneers in Ethically Promoted Colloid Baths

Take an "inside look" at a remarkable advance in topical steroid therapy

The unique base, Veriderm, combined with the outstanding anti-inflammatory steroid, Medrol, provides effective treatment of dermatoses.

Veriderm Medrol Acetate consists of Veriderm, a base closely approximating the composition of normal skin lipids, and Medrol Acetate, the highly effective, dependable corticoid.

Topical use of Veriderm Medrol Acetate produces symptomatic relief and objective improvement of dermatoses, and at the same time aids in correcting dry skin conditions. Veriderm Medrol Acetate, less greasy than an ointment and less drying than a lotion, is indicated in atopic, contact, or seborrheic dermatitis, and in neurodermatitis, anogenital pruritus, and allergic dermatoses.

Available in four formulations: Veriderm Medrol Acetate 0.25% — Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Medrol Acetate 1% is also available.)

For prophylaxis against secondary infection: Veriderm Neo-Medrol Acetate 0.25% — Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Neomycin Sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Neo-Medrol Acetate 1% is also available.)

Administration: After careful cleansing of the affected skin to minimize the possibility of introducing infection, a small amount of either Veriderm Medrol Acetate or Neo-Medrol Acetate is applied and rubbed gently into the involved areas. Application should be made initially one to three times daily. Once control is achieved — usually within a few hours — the frequency of application should be reduced to the minimum necessary to avoid relapses. The 1% preparation is recommended for beginning treatment and the 0.25% preparation for maintenance therapy.

Contraindications: Local application of Veriderm Medrol Acetate or Neo-Medrol Acetate is contraindicated in tuberculosis of the skin and in other cutaneous infections for which an effective antibiotic or chemotherapeutic agent is not available for simultaneous application.

These preparations are usually well tolerated. However, if signs of irritation or sensitivity should develop, application should be discontinued. If bacterial infection should develop during the course of therapy, appropriate local or systemic antibiotic therapy should be instituted.

Supplied in 5 Gm. and 20 Gm. tubes.

Veriderm

Medrol† Acetate

Neo-Medrol† Acetate

TRADEMARK

†TRADEMARK, REG. U. S. PAT. OFF.

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Upjohn

75th year

USES: 'Perazil' relieves the symptoms of sneezing, "incessant" itching, inflamed eyes, rhinorrhea, itching eyes, nose and throat, associated with:
Hay Fever • *Pollenosis* • *Pruritus* • *Urticaria* • *Vasomotor Rhinitis* • *Allergic Dermatitis* • *Drug Sensitivity*

ADVANTAGES: 'Perazil' is both prompt and prolonged in effect, providing symptomatic relief lasting 12 to 24 hours from a single dose.

PRECAUTION: When drowsiness does occur it is generally mild and the usual precautions should be observed. No toxic effects related to either the blood-forming organs or the cardiovascular system are produced.

DOSAGE: Adults and children over 8 years, 50 mg. once or twice daily as required. The dose may be increased in severe cases.

Children from 2 to 8 years, 25 mg. (one sugar-coated tablet) once daily.

Infants up to 2 years, 12½ mg. (one quarter of a 50 mg. tablet) crushed and mixed with a spoonful of jam or syrup.

SUPPLIED: Tablets of 25 mg., sugar-coated, bottles of 100 and 1000; 50 mg., scored, bottles of 100 and 1000.

'PERAZIL'® brand Chlorcyclizine Hydrochloride

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

For effective removal of pollen, smoke, dirt and other irritants

New Honeywell Portable Air Cleaner employs electrostatic precipitation used in laboratories and hospitals to eliminate air contaminants

Honeywell scientists have perfected a portable electrostatic precipitator that will clean the air in an average 12 x 14 foot closed bedroom, office or meeting room once every 15 minutes. Designed to provide cleaner, fresher air, this new unit will remove from the air passing through it, 99% of all pollen as well as 90%* of all airborne dirt, smoke, dust and soot particles as small as 1/850,000 of an inch.

Just as important is its *clean air factor* —(efficiency times air flow). The Honeywell Portable Air Cleaner has a *clean air factor* of 135**. We invite you to compare this figure with that of any other unit presently available.

An activated charcoal filter is also included at no extra cost. Activated charcoal is a well known adsorber of many odors and vapors. This section may be easily removed, if desired.

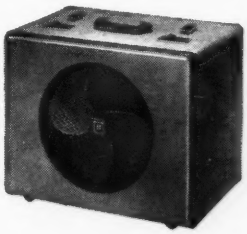
In appearance, the Honeywell Portable resembles a piece of lightweight luggage. It can be moved easily from room to room and plugged into any standard outlet. It will operate for less than a 40 watt lightbulb.

Designed to deliver today's highest practical efficiency, the Honeywell Portable Electronic Air Cleaner is necessarily more expensive than other portables. A product of Honeywell's research laboratories, it is backed by Honeywell service staffs in over 112 cities, and fully guaranteed. It is now available at selected physician-hospital supply and office supply distributors. It is also available on a rental basis from leading physician and hospital supply rental agencies. For more complete information, write Honeywell, Dept. JL-7-104, Minneapolis 8, Minnesota. *Sales and service offices in all principal cities of the world.*

Price $229.95

Honeywell

H HONEYWELL SINCE 1885 *First in Control*



**As measured by National Bureau of Standards Dust Spot Method*

***Slightly less with charcoal filter*

Where's the arthritic this morning?

Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	**12 to 16 mg.**	**6 to 12 mg.**
Moderately severe	**8 to 10 mg.**	**4 to 8 mg.**
Moderate	**6 to 8 mg.**	**2 to 6 mg.**
Children	**6 to 10 mg.**	**2 to 8 mg.**

With Medrol Medules, it may be possible to reduce the total daily dose by ⅓.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Each capsule contains: Medrol (methylprednisolone) 2 mg. or 4 mg.
Supplied in bottles of 30 and 100.

Medrol Medules

Upjohn *75th year*

*TRADEMARK, REG. U.S. PAT. OFF. COPYRIGHT 1961, THE UPJOHN COMPANY JUNE, 1961 THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Schering

Perhaps you have hesitated to prescribe the benefits of a topical steroid because of concern about effectiveness or high cost.

Perhaps you have felt that the usual packaging of topical steroids provides inadequate, uneconomical quantities to suffice for a complete course of treatment.

If any of these considerations reflects your thinking, we believe you will be interested to learn that a truly effective and reasonably priced topical steroid now is available for your patients with dermatologic disorders... DILODERM™ Cream (brand of dichlorisone acetate).

As to effectiveness, here is what a recent report* stated on the use of DILODERM in 53 cases of poison ivy dermatitis: "A satisfactory response...was seen in all cases. There were no cases of primary irritation or other side effects...."

As a matter of fact...you will find not only that DILODERM Cream is exceptionally beneficial in a wide variety of dermatoses responsive to topical steroids, but also that it costs *less* in most instances than generic hydrocortisone creams. In addition, DILODERM affords even greater savings over other topical steroids. Actually, the 15 Gm. tube of DILODERM Cream costs less than virtually all all other topical steroid preparations now prescribed.

As a matter of economy...the 15 Gm. tube of DILODERM is ideally suited for the treatment of large skin areas or extensive lesions. It *covers more* with *less waste;* it provides three times as much medication for only slightly more than double the cost of a small 5 Gm. tube of unbranded hydrocortisone.

We believe your patients with dermatoses will appreciate the significant savings DILODERM Cream affords, and that you, too, will agree... DILODERM in the 15 Gm. tube is *effective, economical in price,* and *even more economical in use.*

Also available: DILODERM Cream, 5 Gm. tube; NEO-DILODERM® Cream 0.25%, 5 and 15 Gm. tubes; DILODERM and NEO-DILODERM Foam, 10 Gm. dispensers; DILODERM and NEO-DILODERM Aerosols, 50 Gm. containers.

*Gant, J. Q., Jr.: *M. Ann. District of Columbia 30*:267, 1961.

If concern about effectiveness or high cost has kept you from prescribing any topical steroid...

THESE FACTS MAY CHANGE YOUR MIND

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

S-866

Super-Oiled

Oilatum® Soap

hypoallergenic cleanser

for tender, sensitive skin.

- Super-oiled (not super-fatted) to minimize "drying"
- 600% higher content of unsaturated oils than other cleansers
- Rich, oil-laden lather, even in hard water
- Ideal for pediatric and geriatric use
- Available scented or unscented

COMPLEMENT *DON'T COMPLICATE* SKIN TREATMENT

Super-moisturized

Oilatum® Cream

(new improved formula)

for dry, thirsty skin.

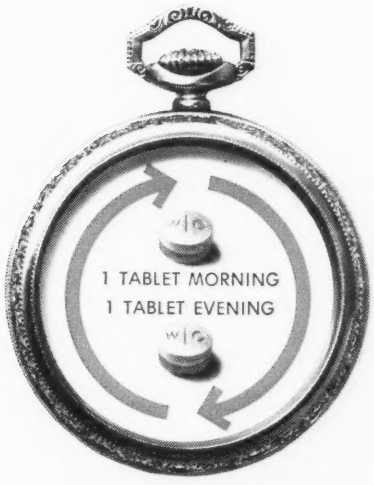
- An oil-in-water emulsion buffered to pH 5.5
- Leaves "the film that breathes" . . . retards moisture loss
- Contains highly unsaturated vegetable oils . . . no lanolin or mineral oil
- Cosmetically pleasant . . . scented or unscented

You can recommend STIEFEL Oilatum Cream with confidence for symptomatic therapy of dry, tender or sensitive skin, lanolin or alkali-sensitivity, ichthyosis, winter itch, wind burn and similar etiologic entities.

STIEFEL
LABORATORIES, INC.
Oak Hill, New York
Canada: Winley Morris, Montreal
Logical Dermatologicals—Since 1847

Samples & literature of Oilatum Soap & Oilatum Cream sent on request.

all it takes for sustained protection in asthma



all-day and all-night relief from asthma symptoms

New Tedral SA

Sustained Action antiasthmatic

One tablet on arising—protects through the working day, virtually eliminates the need for emergency medication

One tablet 12 hours later—lets the patient sleep, reduces the need for middle-of-the-night emergency medication

New Tedral SA protects against bronchial constriction and reduces mucous congestion throughout the day and night, increases vital capacity and ability to exhale, reduces the frequency and severity of asthmatic attacks. Patients get the benefits of sustained protection with the convenience of b.i.d. dosage. New Tedral SA is particularly indicated for patients who need continuous medication over prolonged periods.

RECOMMENDED ADULT DOSAGE: 1 tablet on arising and 1 tablet 12 hours later.

PRECAUTIONS: Tedral SA should be used with caution in patients with cardiovascular disease and/or severe hypertension, circulatory collapse, hyperthyroidism, prostatic hypertrophy or glaucoma. Phenobarbital in the formula may be habit forming.

EACH TABLET CONTAINS: Theophylline, 180 mg.; Ephedrine HCl, 48 mg.; Phenobarbital, 25 mg. Tedral SA is available to your patients on prescription only.

WARNER
CHILCOTT
MORRIS PLAINS, N.J.

GP12

makers of Tedral Gelusil Mandelamine Peritrate Proloid

These
"Cold-Weather Allergies"
respond well to

ALGIC®
antihistaminic/tranquilizer/decongestant

allergic rhinitis
sinusitis
bronchitis
cough
allergic manifestations of the
"common cold"

For allergies

℞

ALGIC®

whatever the site, whatever the season

Algic is comprehensive symptomatic therapy for the allergic patient: antihistaminic/tranquilizer/decongestant. It can be prescribed without the usual concern about side effects, such as drowsiness and jitters.

Only ALGIC and new ALGIC-S.A. provide three essential effects in a single tablet...

ALGIC™

NEW ALGIC–S.A.

Sustained Action

Antihistaminic / tranquilizer / decongestant

The comprehensive therapy for the allergic patient

— **prevents allergic manifestations**
— **allays patient anxiety**
— **decongests swollen tissues**

"The very nature of the formula predicts its effectiveness in allergic diseases."[1]

"Algic is highly effective in symptomatic therapy."
"82% experienced marked therapeutic effect."[2]

Usual Adult Dosage:

Algic	1 to 2 tablets every 4 hours.
Algic-S.A.	1 tablet every 8 to 10 hours.

Children (6-12): one-half adult dosage.

Each scored tablet contains:	Algic	Algic-S.A.
Chlorpheniramine Maleate	3 mg.	6 mg.
Phenyltoloxamine Dihydrogen Citrate	50 mg.	100 mg.
Racephedrine Hydrochloride	30 mg.	60 mg.

(1) St. John, M. A., Shure, N. and Gaynes, H. E., "Appraisal of a New Anti-Allergy Compound", Ann. Allergy 19:157, 1961. (2) Swartz, H., "Clinical Evaluation of a New Drug (Algic) in the Symptomatic Therapy of Perennial Allergic Coryza" Curr. Ther. Res. 2:327-332, 1960.

SPENCER Laboratories, Inc., Morristown, New Jersey

If "jitters" limit dosage for your ASTHMA patient

℞ **EPHOXAMINE®**

Bronchodilator/tranquilizer

TABLETS – PEDIATRIC SYRUP

—provides full bronchodilator potency
—1/6th of the CNS stimulation liability

The bronchodilator actions of Racephedrine and Ephedrine are equal.[2]

The clinical (official) doses are the same.

Pharmacological studies by Schulte, et al[3] in which the central excitatory effects of Racephedrine and Ephedrine are compared show *Racephedrine has 1/6th the central nervous system side-effects liability of Ephedrine.*

"Ephoxamine has been found to be a *highly useful asthmalytic* preparation, which seems to be effective when the usual, oral asthmalytics are not." [1]

Suggested Dosage: Syrup — Children 2-4 yrs., ½-1 tsp.; 4-7 yrs., 1-2 tsp. every 4 hours. Tablets (scored) — Children 6-12 yrs., ½-1 tablet; Adults 1-2 tablets every 4 hours.

One tsp. of syrup is equal to ¼ tablet. Each scored tablet contains: 50 mg. Phenyltoloxamine DHC and 30 mg. Racephedrine HCl.

Contraindications: Usual care in the use of sympathomimetics in patients with hypertension, hyperthyroidism, diabetes, and heart disease should be exercised.

1. Swartz, H., "Ephoxamine in the Symptomatic Therapy of Bronchial Asthma" Current Therapeutic Research, 1:3; Nov. 1959.
2. Goodman and Gilman, "The Pharmacological Basis of Therapeutics" the Macmillan Company, 1958.
3. Schulte, J. W., Reif, E. C., Bacher, Jr., J. A., Lawrence, W. S., and Tainter, M. L., J. Pharmacol. Exp. Ther., 11:62-74.

SPENCER Laboratories, Inc., Morristown, New Jersey

Advertisement

A Racephedrine-Phenyltoloxamine-Containing Compound (Ephoxamine) in the Treatment of Bronchial Asthma, by Nicholas J. Tapay, M.D., Pediatric and Adult Allergy Clinics, the University of Kansas Medical Center, Kansas City, Kansas, and Children's Mercy Hospital, Kansas City, Missouri.

"Expert symptomatic management means the proper selection of suitable drugs which are without adverse side reactions, with sufficiently sustained effect and with minimal likelihood of development of tolerance.

"The compound tried in the present study is identified as Ephoxamine. Each scored tablet contained 25 mg. of racephedrine hydrochloride and 50 mg. of phenyltoloxamine dihydrogen citrate. One teaspoonful of the syrup formulation was equal to ¼ tablets.

"Racephedrine as a sympathomimetic amine counteracts bronchospasm, glandular hypersecretion and mucosal edema. Phenyltoloxamine alleviates anxiety and tension in addition to its antihistaminic and milder anti-spasmodic activity. This formula seems to offer a combined type of treatment embracing both the physical (allergic) and emotional factors involved.

"The purpose of this study was fourfold: (1) To determine the efficiency of Ephoxamine in relieving milder and moderately severe acute attacks . . . (2) To evaluate its clinical usefulness in the light of side reactions developed . . . (3) To see how often the same patient material experienced undesirable side effects due to the drug used prior to medication with Ephoxamine.

"(4) To compare its value to those of other symptomatic drugs based either upon the parent's observation or the patients' own experience.

TABLE I—RESULTS OF TREATMENT WITH EPHOXAMINE IN 75 PATIENTS

Clinical Results	Children	Adults	Total
Efficacy:			
Found it effective	45	16	61 (81.3%)
Found it ineffective	10	4	14 (18.6%)
Side reactions:			
Drowsiness	1	1	2 (2.6%)
Drying effect	4	3	7 (9.3%)
Pressor effect	—	—	—
Nausea, vomiting	—	—	—

"Conclusions:

1. Ephoxamine, a racephedrine-phenyltoloxamine-containing compound has been used with 81% efficiency in relieving acute asthmatic attacks both in children and in adults.
2. It possesses one-third the side effect liability of ephedrine-barbiturate compounds.
3. Since sympathomimetic pressor effects are virtually absent, Ephoxamine appears to be the drug of choice in asthmatic patients with hypertension or heart disease, and in chronic asthma requiring maintenance medication. For the same reason it should be tried in the treatment of those asthmatic patients who are unable to take ephedrine.
4. In those few cases where side reactions occurred, these effects could be attributed to the soporific action of phenyltoloxamine."

Excerpted from Current Therapeutic Research, Vol. 3, No. 7, of July, 1961
a service of SPENCER LABORATORIES, INC., Morristown, N. J.

for infants allergic to cow's milk

a modern milk substitute

meeting the exacting requirements of your pediatric practice

Diagnostic Aid. A simple trial with Sobee for 2 or 3 days, to determine if milk is the offending food, may eliminate the need for further, more complicated diagnostic procedures. Evidence of symptomatic relief indicates continued treatment with Sobee.

Balanced Nutrition. Sobee supplies 19% of its calories from soya protein, 35% from fat and 46% from carbohydrate. Hypoallergenic fat-soluble vitamins are added. With Sobee, "The growth rates were normal or above normal in comparison with other infants of the same age."[1]

Good Stool Pattern. In a study of 102 infants on Sobee, the number of stools ranged from 1 to 4 per day.[1] Soya stools are bulkier than cow's milk stools. Constipation is infrequent.

Excellent Acceptance. Sobee is rich and creamy without a "burned-bean" flavor or chalky after-taste. Acceptance of Sobee, "both by infants and mothers, was excellent."[1]

1. Kahn, S.: Am. Pract. & Digest Treat. 8:65 (Jan.) 1957.

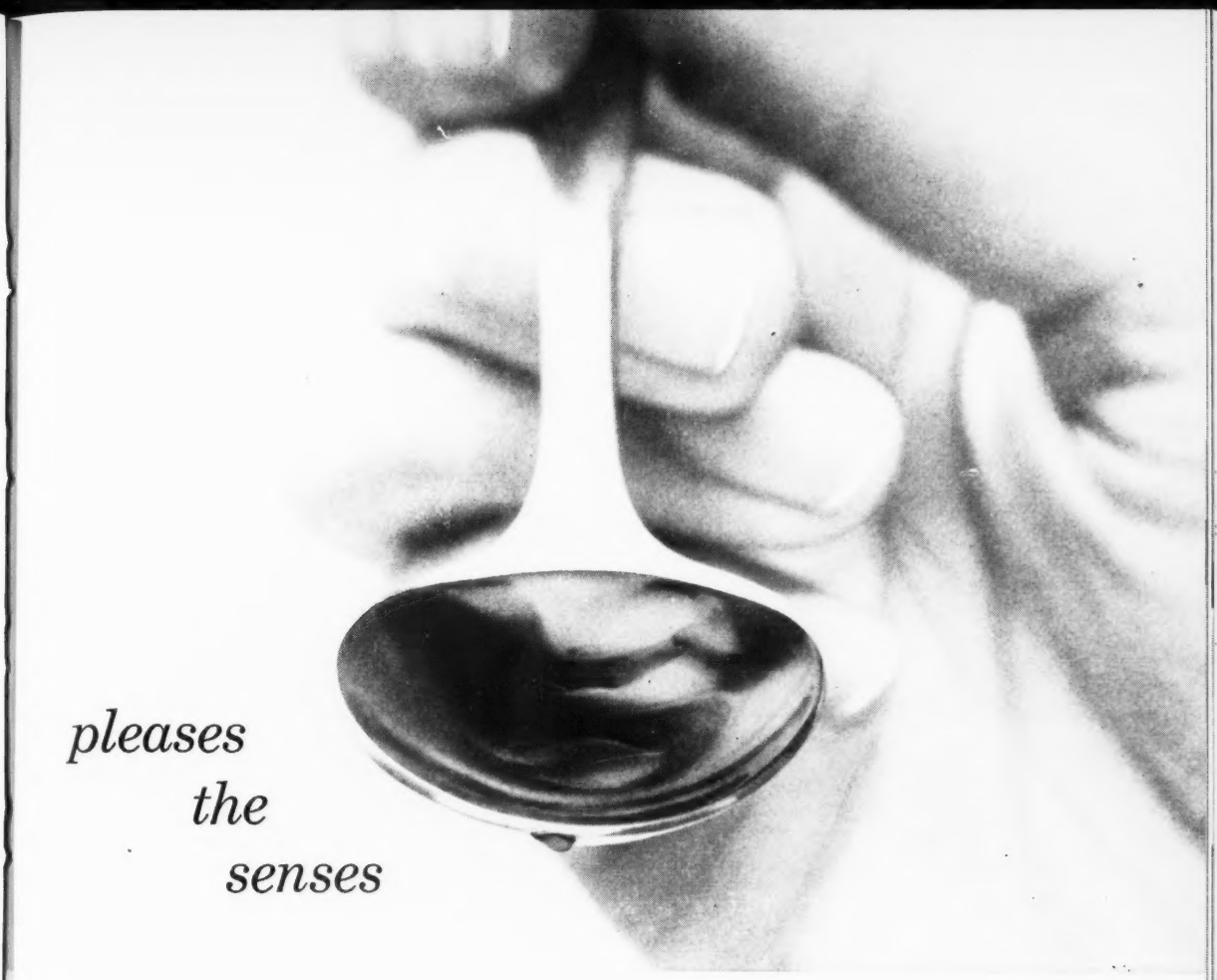
specify

Sobee®

Milk-free soya formula

Mead Johnson Laboratories

Symbol of service in medicine



pleases the senses

...as it eases the respiratory allergy

NORISODRINE® syrup

with calcium iodide

Whether he's afflicted with allergic sniffle or outright asthma, a cooperative patient can mean half the battle. That's why a treatment that's no chore to take can be so important. And that's what you get in Norisodrine Syrup.

You'll find, first, with Norisodrine Syrup a bronchodilator-expectorant useful in controlling a wide range of respiratory allergies. You'll *also* find that there's nothing easier on the senses than Norisodrine Syrup—golden color, fresh mint taste, pleasant smell.

Time and again, Norisodrine Syrup's value has been proved in patients with chronic cough, wheeze, or other classic asthma symptoms.

In a study[1] covering the treatment of 150 patients —ranging in age from one to seventy-three years— 133 reported good to excellent results.

Conclusions were: "Norisodrine Syrup diminished cough, brought about easy expectoration of mucus from the bronchial tree, lessened tightness in the chest, improved respiration."

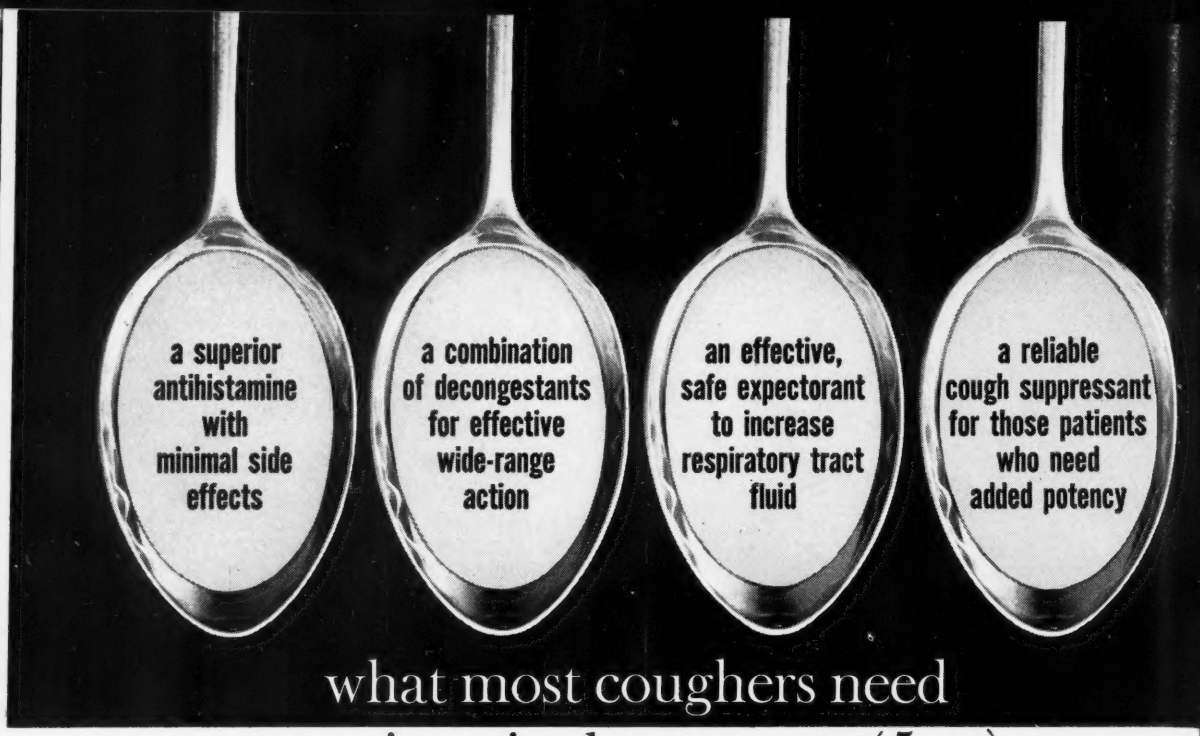
Consider good-tasting Norisodrine Syrup for your next respiratory allergy patient. It can help you manage symptoms that have been troublesome for years.

[1]Frohman, I. P., A New Antitussive Agent, M. Times, 88:924, Aug. 1960.

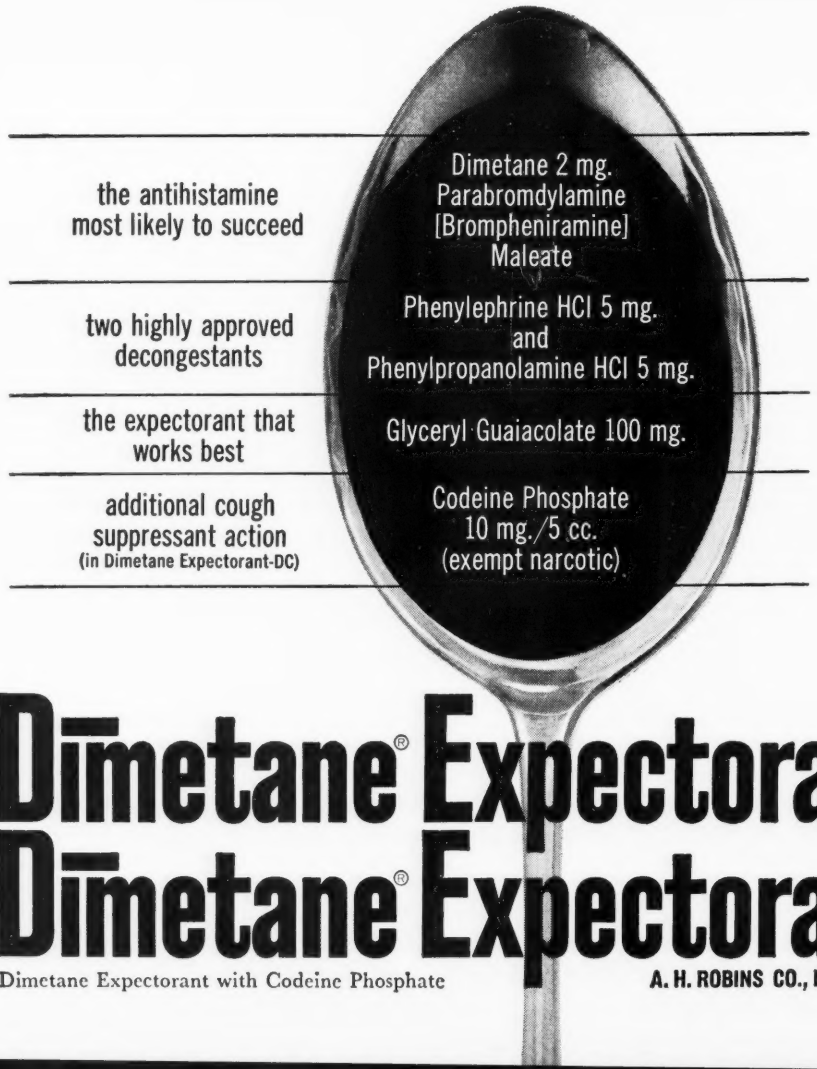
Norisodrine: Isoproterenol Sulfate, Abbott.

ABBOTT

109041


a superior antihistamine with minimal side effects
a combination of decongestants for effective wide-range action
an effective, safe expectorant to increase respiratory tract fluid
a reliable cough suppressant for those patients who need added potency

what most coughers need now in a single teaspoon (5 cc.)


the antihistamine most likely to succeed
Dimetane 2 mg. Parabromdylamine [Brompheniramine] Maleate
two highly approved decongestants
Phenylephrine HCl 5 mg. and Phenylpropanolamine HCl 5 mg.
the expectorant that works best
Glyceryl Guaiacolate 100 mg.
additional cough suppressant action (in Dimetane Expectorant-DC)
Codeine Phosphate 10 mg./5 cc. (exempt narcotic)

Dimetane® Expectorant
Dimetane® Expectorant-DC

PHARMACEUTICALS RESEARCH

Dimetane Expectorant with Codeine Phosphate

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

WHY ACID MANTLE?

A DISTINCT THERAPEUTIC ENTITY*
Restores and maintains skin's normal protective acidity—
speeds natural healing and helps sensitive skin resist irritants and infection.

A NOTABLE VEHICLE
Special water-miscible, evaporable base assures better dispersion,
greater concentration of active ingredients in contact with skin—
increases response through its own therapeutic action.

*Supplied: in Creme and Lotion (pH 4.6).

now low-cost steroid topicals help insure sustained improvement without setbacks

new 1/8% Cort-Dome

Creme • Lotion (pH 4.6)

micro-dispersed hydrocortisone alcohol in Acid Mantle® for economical long-term therapy

IMPROVED PROCESS PERMITS EFFICIENT DOSAGE REDUCTION Once the dermatosis is brought under control with higher steroid concentrations, new ⅛% Cort-Dome, potentiated by the *micro-dispersion* of hydrocortisone in its Acid Mantle vehicle, can help insure therapeutic success—with less likelihood of flare-ups—until the skin's natural defenses are restored. The markedly lower cost of ⅛% Cort-Dome adds assurance that the patient will continue therapy as directed.

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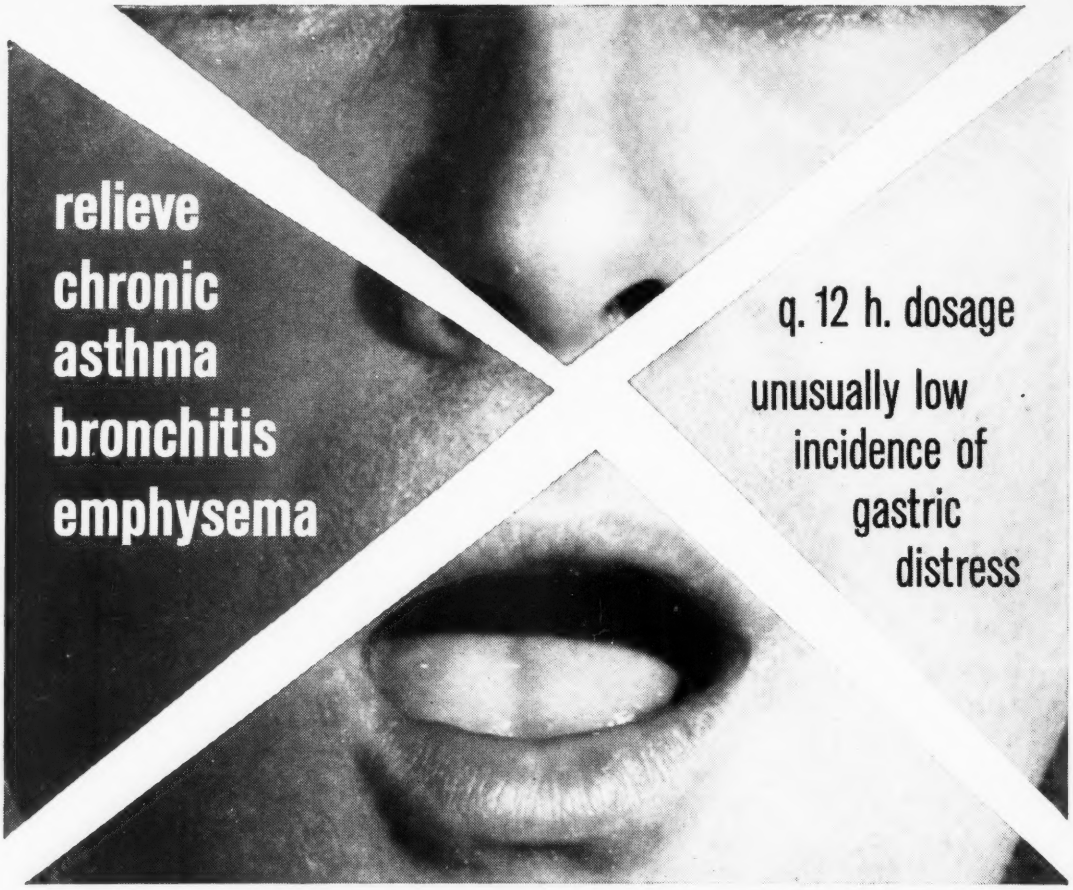

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Oral Sustained Medication* Aminophylline 4½ gr. (.3 Gm.)

Patients breathe easier all day, sleep better all night as each dose of Aminophylline Dura-Tabs provides effective blood levels for up to 12 hours. Few patients experience gastric distress since only a fraction of the daily dosage contacts the stomach. Economical, convenient, well tolerated, Aminophylline Dura-Tabs...

eases bronchospasm, reduces bronchial edema, increases breathing capacity

Other indications: congestive heart failure, angina pectoris, paroxysmal dyspnea, Cheyne-Stokes respiration.

Dosage: Adults, 1 to 2 Aminophylline Dura-Tabs q. 12 h.; Children under 10, one-half Aminophylline Dura-Tabs q. 8 to 10 h. Bottles of 30, 100, 250 scored Dura-Tabs.

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ALLERGEX* AEROSOL

for spraying

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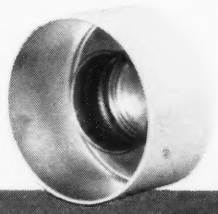

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subdues inflammation and edema in acute or chronic dermatoses[1,2]

Chymoral may be employed to excellent advantage for control of the inflamed and weeping lesions of acute dermatoses, as well as for subacute and chronic conditions. Used either as the sole agent or as an adjunct to standard topical and systemic therapies, Chymoral modifies inflammatory reaction, helps improve regional blood flow, and dissipates edema. It may therefore assist the skin's own reparative attempts in such conditions as acne, ulcerations, furunculosis, abscesses, otitis externa, burns, and acute eczema or chronic atopic dermatitis.

1. Clinical Reports to the Medical Director, Armour Pharmaceutical Company, 1960. 2. Teitel, L. H., *et al.:* Med. *29:*150, 1960.

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Chymoral is an ORAL anti-inflammatory enzyme tablet specifically formulated for intestinal absorption. Each tablet provides enzymatic activity, equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravasates; helps to liquefy thick tenacious mucous secretions; improves regional circulation; promotes healing; reduces pain. INDICATIONS: Chymoral is indicated in respiratory conditions such as asthma, bronchitis, rhinitis, sinusitis; in accidental trauma to speed absorption of hematoma, bruises, and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions such as pelvic inflammatory disease and mastitis; in obstetrics as episiotomies and breast engorgement; in surgical procedures as biopsies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disorders as epididymitis, orchitis and prostatitis; in dental and oral surgery as fractures of the mandible or maxilla, difficult or multiple extractions, and alveolectomies. CONTRAINDICATIONS: None known. INCOMPATIBILITIES: None known. Antibiotics as well as generally accepted measures may be coadministered. SIDE EFFECTS: Mild gastric upsets, rarely encountered. DOSAGE: Recommended initial dose is two tablets q.i.d.; one tablet q.i.d. for maintenance. SUPPLIED: Bottles of 48 and 250 tablets.

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amino acid/antiseptic
with Liquor Carbonis Detergens

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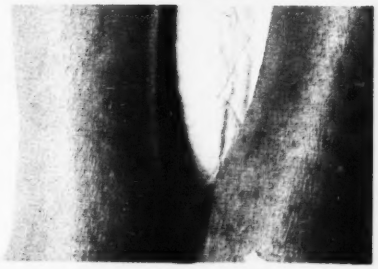

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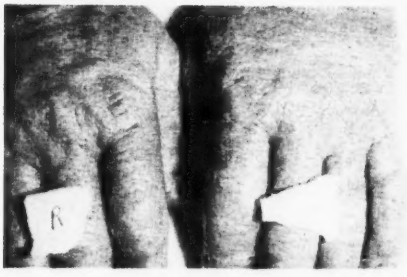

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*Wise, L. J., Jr., and Derbes, V. J.: Evaluation of Methatar in eczema. South. M. J. 54:1031, Sept., 1961.

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relieves itching and burning and promotes healing through the tissue-regenerative action of a protein hydrolysate reinforced by the amino acid, methionine

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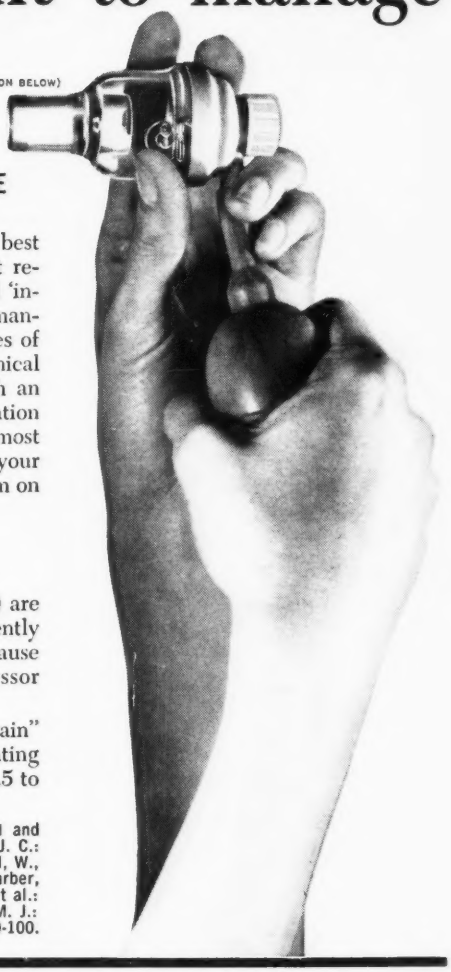

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SUPPLIED: Solution, bottles of 7.5, 15 and 30 cc.; Nebulizers, Standard and Pocket size. Also Aerosol Unit. REFERENCES: 1. Digilio, V. A., and Munch, J. C.: Ann. Allergy 13:257, 1955. 2. Bickerman, H. A., and Barach, A. L., in Modell, W., Ed.: Drugs of Choice, St. Louis, The C. V. Mosby Co., 1958-59, p. 582. 3. Farber, S. M., and Wilson, R. H. L.: Ann. Int. Med. 50:1241, 1959. 4. Munch, J. C., et al.: J. Am. Pharm. A. (Scient. Ed.) 40:526, 1951. 5. Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema, New York, Grune & Stratton, 1953, pp. 99-100.
*Bibliography available on request.

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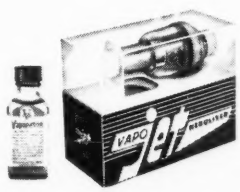

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(1) Silbert, N. E., Ciba Clinical Symposia; 6: 86: May 1954

(2) Mechaneck, I., Annals of Allergy; 12: 164: March 1954

(3) Rosen, F. L., J. Med. Soc. N.J., 51: 110: March 1954

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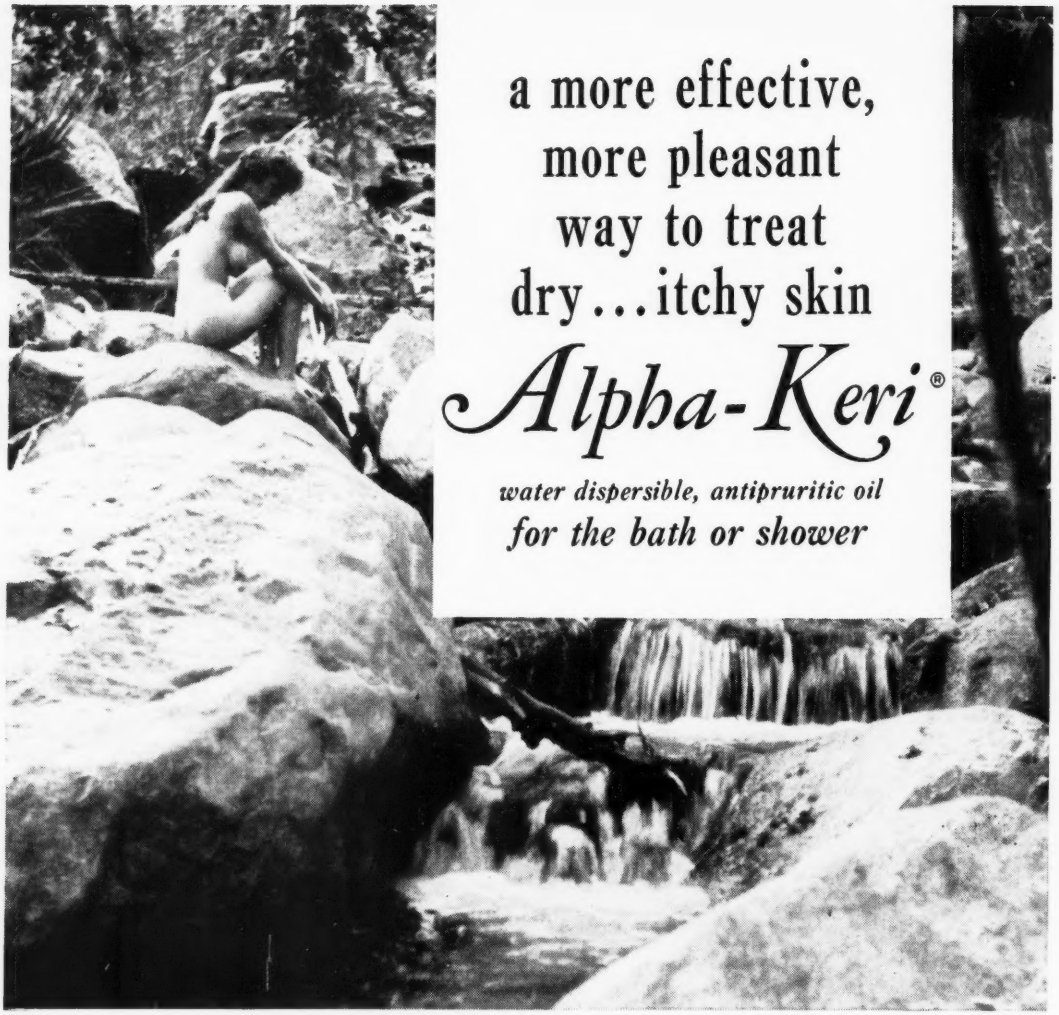

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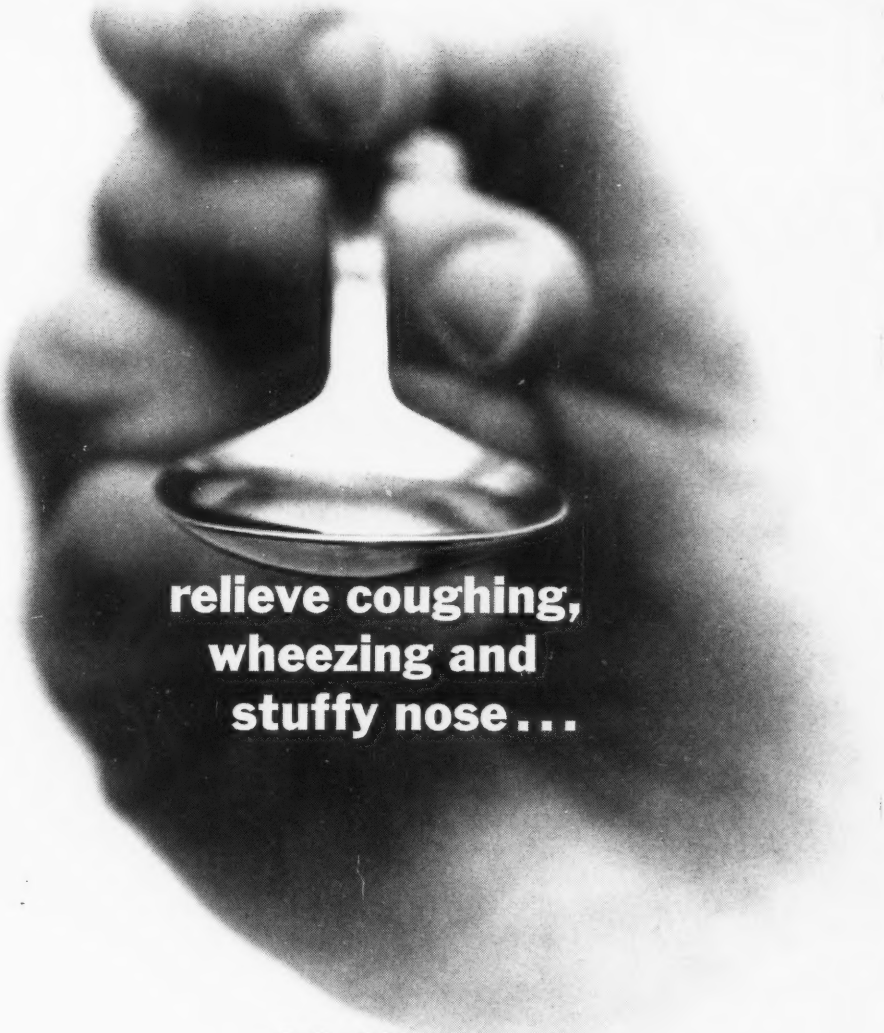

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'Actidil'® brand Triprolidine Hydrochloride	2 mg.
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Dosage: Adults and children over 12 years—2 tsp., 4 times daily. Children 6 to 12 years—1 tsp., 4 times daily. Infants and children up to 6 years—½ tsp., 4 times daily.

Precaution: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride produces only a low incidence of drowsiness, appropriate precautions should be observed.

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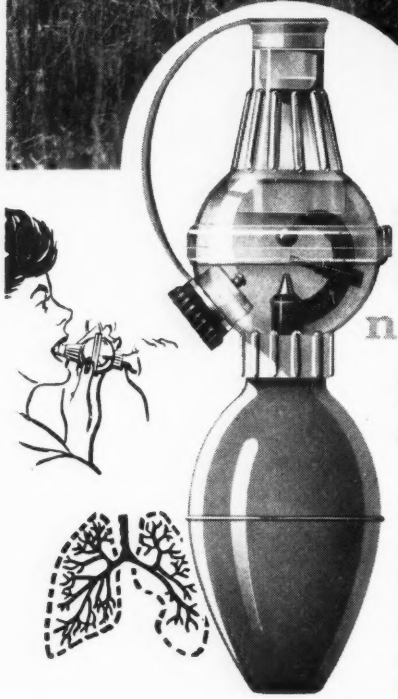

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[1]*References: ABRAMSON, H. A.: "Principles and Practice of Aerosol Therapy of the Lungs and Bronchi", Annals of Allergy, Vol. 4, Nov.-Dec., 1946. BARACH, A. L., GARWAITHE, B., and RULE, C: "Penicillin aerosol in bronchio-pulmonary and sinus infections", New York State J. Med., 46:1703, 1946. MITCHELL, R. I., "Retention of Aerosol Particles in the Respiratory Tract", Am. Rev. Resp. Diseases, 82:672, 1960.*

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Itching in children can now be controlled on b.i.d. dosage with a long-acting[1] antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking. They can also benefit by the effectiveness of Tacaryl Hydrochloride in controlling symptoms in a wide variety of allergic conditions,[2-8] including hay fever and perennial rhinitis.

dosage: One Chewable Tablet (3.6 mg.) twice daily. Adjustment of dose or interval may be desirable for some patients.

contraindications: There are no known contraindications.

side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence... though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

references: (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

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By MORRIS LEIDER, M.D., Associate Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School, New York, N. Y. Published September, 1961. 2nd edition, 437 pages, 6¾″ x 9¾″, 280 photographs, 15 drawings. Price, $13.75.

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Not objectively, as the BMR can be measured by vital capacity tests.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

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75th year

See page 15 for description, indications, dosage, precautions, side effects, and how supplied.

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*Glaser, J.: Ann. Allergy 18:150 (May) 1960.

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References: 1. Grater, W.C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. 6:(No. 3) 181, 1959.

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4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
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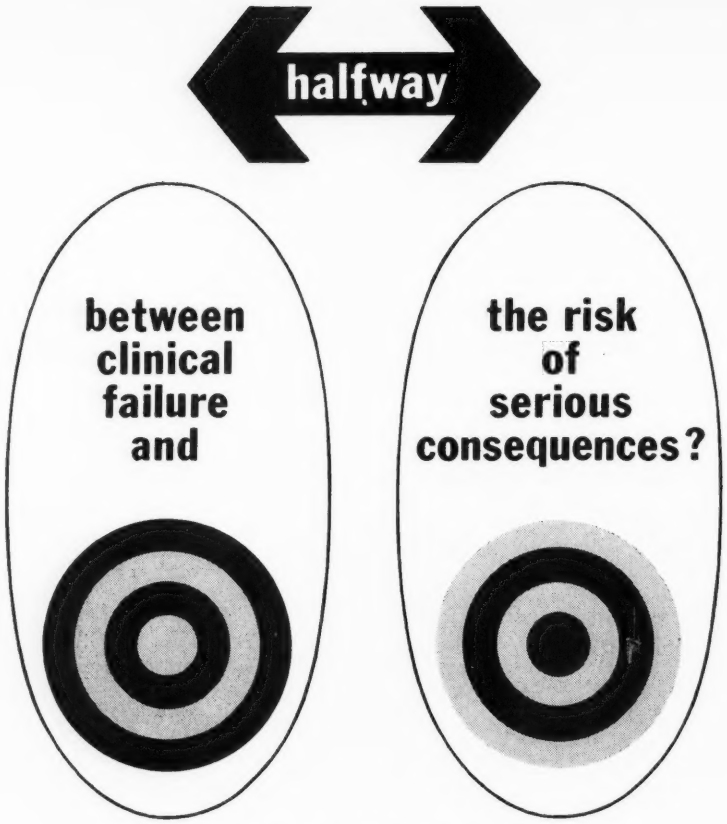
7th day	RETURN VISIT	



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1. Randolph, T. G.: Ann. Allergy *8*:626 (Sept.-Oct.) 1950. 2. Zindler, G. A.: Ann. Allergy *9*:494 (July-Aug.) 1951. 3. Wittich, F. W.: Ann. Allergy *9*:502 (July-Aug.) 1951. 4. Prince, H. E., and Etter, R. L.: Letters of Int. Correspondence Soc. of Allergists Series XVII:17 (1953). 5. Fenton, N. M.: Ann. Allergy *11*:336 (May-June) 1953. 6. Aronoff, S., and Ghaemi, A.: J. M. Soc. New Jersey *50*:564 (Dec.) 1953. 7. Randolph, T. G.: M. Clinics North America *38*: (Mar.) 1954. 8. Knight, G. F.: Ann. Allergy *12*:174 (March-April) 1954. 9. Leech, C. A., Jr.: Clinical Med. *62*: (Mar.) 1955. 10. Rinkle, H. J.: In Conn. H. F., Current Therapy 1959, Philadelphia, W. B. Saunders, 1959, p. 406. 11. Meyer-Rohn, J., and Vogel, A.: Arch. klin. u. exper. Derm. *210*:372, 1960.

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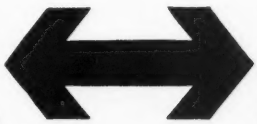

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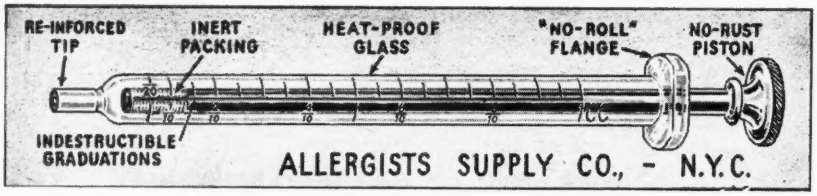

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Bibliography: 1. Blumenthal, L.S. and Fuchs, M., Am. J. Gasterol., *33*, 189-202, 1960. 2. Ryan, R.E., Med. Times, *88*, 6, 739-742, 1960. 3. Segal, M.S., J.A.M.A., *169*:1063-1071, 1959. Write Professional Service Department for literature and trial supply.

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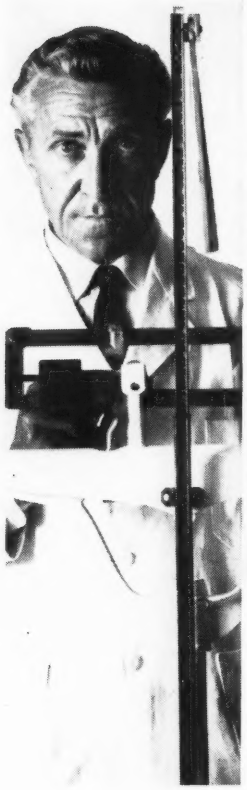

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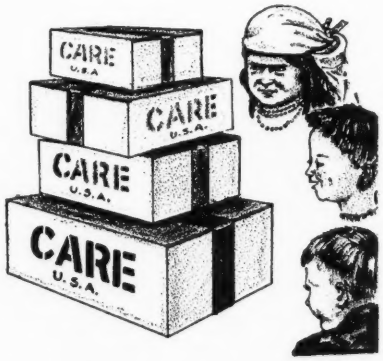

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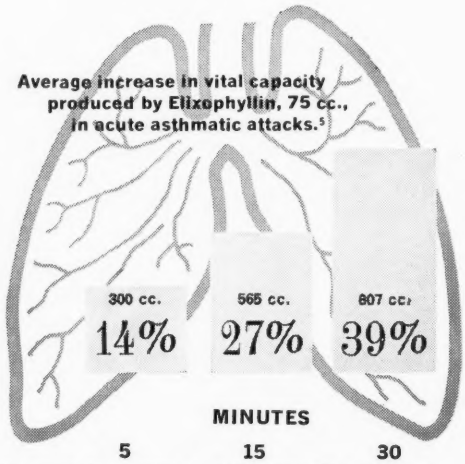

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1. Nelson, L. S., and Stoesser, A. V.: Ann. Allergy 11:572-579 (Sept.-Oct.) 1953.

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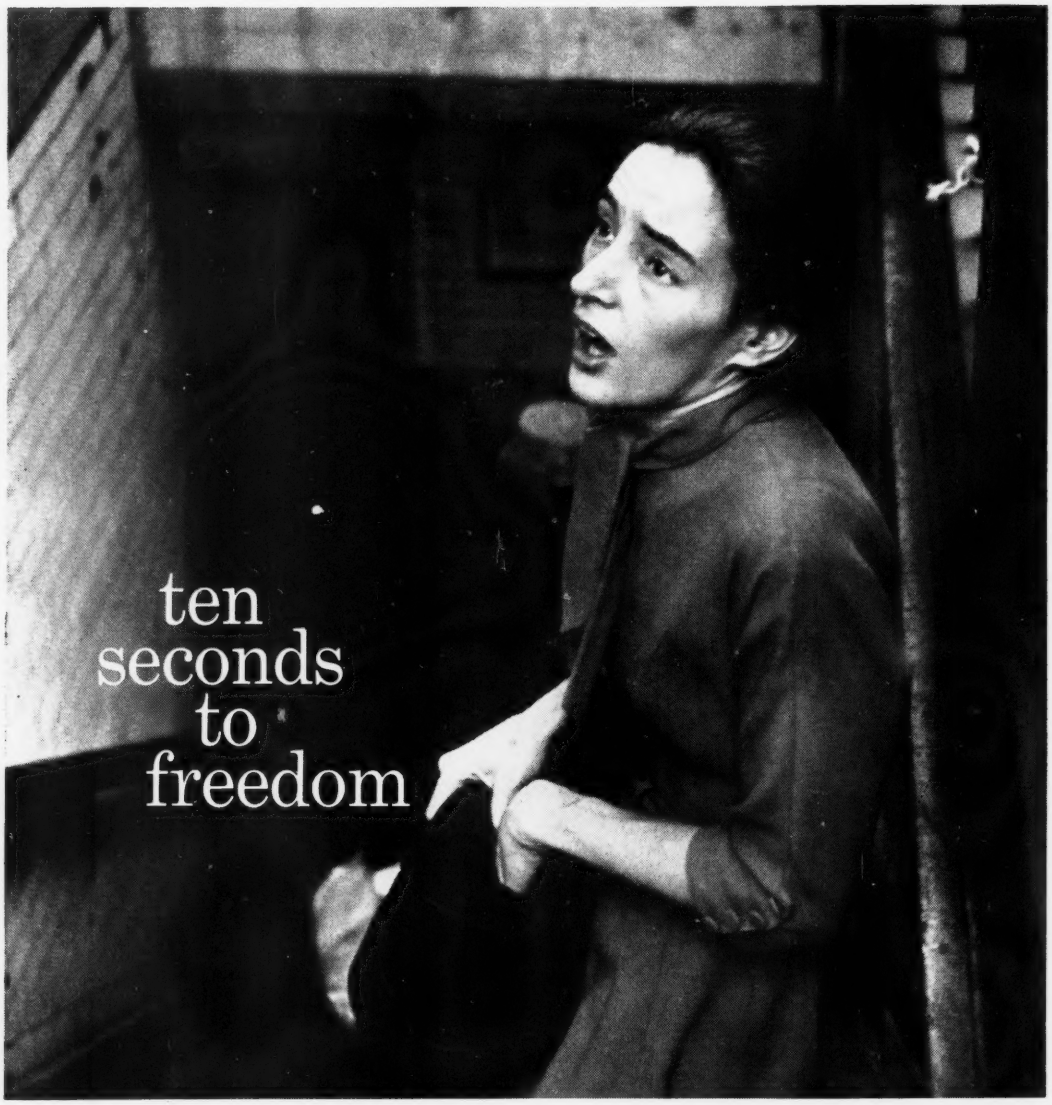

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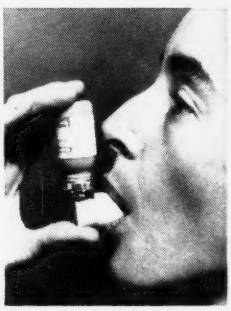

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